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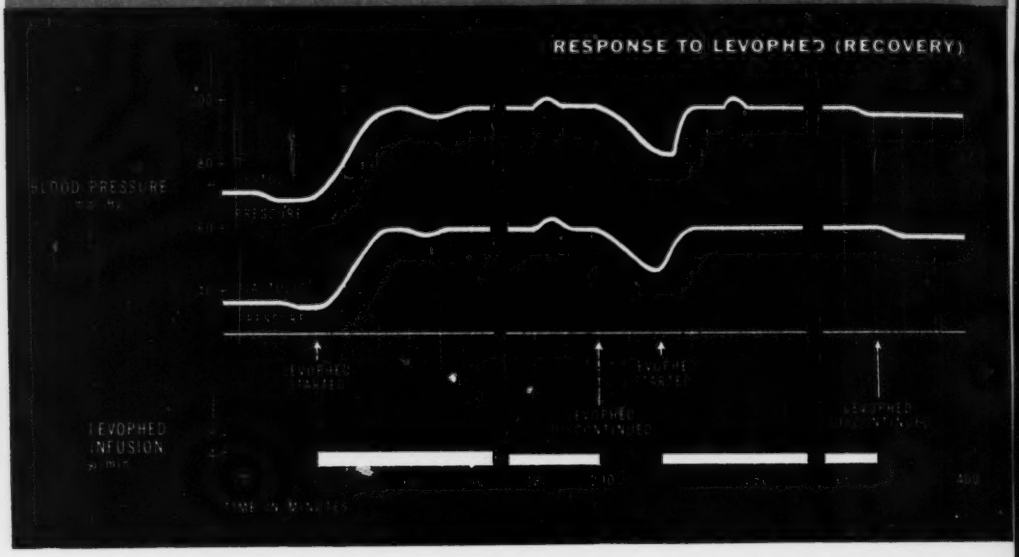
Myocardial Infarction with Severe Shock:



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"... in correcting the state of shock we have enabled certain patients to recover from the initial episode, which otherwise gave every indication of culminating in death."[1]

Levophed infusion causes a striking rise in oxygen tension in areas of myocardial ischemia produced by coronary obstruction.[2] "It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date."[3]

"Severe cardiogenic shock demands therapy... the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Electric Alternans in Pericardial Effusion

By MAURICE MC GREGOR, B. CH., M.D., M.R.C.P., AND EUGENE BASKIND, B.CH., M.D.

Evidence is presented which indicates that electric alternation is frequently associated with pericardial effusion; that this alternation is of a unique type; and that it is caused by movement of the heart in the fluid filled pericardial sac.

IN 1946 one of us observed and reported[1] a case of pericardial effusion with simultaneous electric alternans of the auricles and ventricles and in the following year noticed a publication illustrating the same electric phenomenon in a similar case[2] (see fig. 1A and B). Some time later the other author of this paper (E. B.) while studying a series of cases of pericarditis with effusion remarked on the occurrence both of alternans and of less regular non-respiratory fluctuations in amplitude of the ventricular complexes and postulated that they arose from the free movement of the heart suspended in fluid.[3] Observations made at that time and more recently, together with a scrutiny of the cases reported in the literature, has led us to conclude, first, that there is an association between electric alternans and effusion which is more than fortuitous and second, that there are some unique features of the alternans which is found in cases of effusion. Finally it has led us to suggest a mechanism for the electric alternation in these cases which supposes the free movement of the heart in the fluid filled pericardial sac.

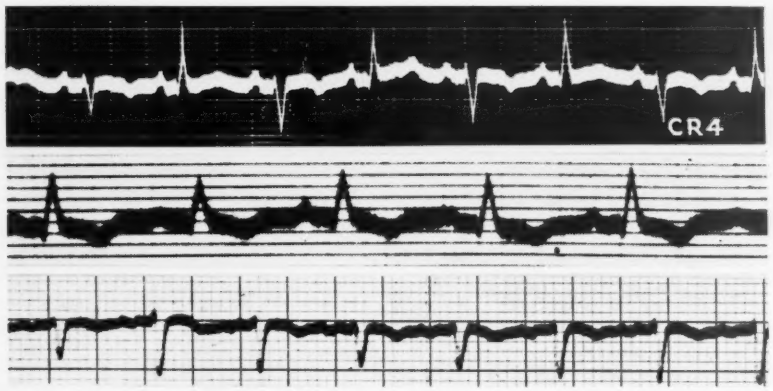

FIG. 1. A. Simultaneous alternation of auricular and ventricular complexes.[1] Lead CR4. B. Simultaneous alternation of auricular and ventricular complexes.[2] Lead II. C. Fluctuation of voltage during respiratory arrest. Lead V_1.

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Electric alternation of the ventricular complexes can be divided into three main groups; a group associated with very rapid

TABLE 1.—*The Probable Diagnosis in 27 Published Cases of Ventricular Alternans*

Author	Case	Diagnosis
Traut[13]	1	Acute pericard. with effusion
Wood[17]	1*	Pericard. malignancy
Risinger et al.[16]	1*	Malignant hemopericard.
Fletcher[2]	1*	Malignant pericard. effusion
McGregor[1]	1*	Tubere. pericard. effusion
Feldman[20]	1	Malignant hemopericard.
Hamburger et al.[7]	1	Ischemia
	2*	Malignant pericard. effusion
Brody[15]	1	Hypertension
	2	Rheumatic heart disease
Kalter, Schwartz[9]	1	Acute pericard. Probable effusion
	2	Syphilis Congest. fail.
	3	Cor pulmonale. Congest. fail.
	5	Pneumonia. Congest. fail.
Kalter, Grishman[4]	7	Syphilitic Miliary tubere.
	9	Ischemia. Congest. fail.
	10	Unknown
	11*	Suppurative pericard. effusion
	13	Rheumatic pericard. Congest. fail.
	14	Ischemia ? Pericard.?
	15	Rheumatic heart dis. Pulmon., embolism
	16	Hypertensive. Ischemia
Groedel, Miller[18]	1	Ischemia? Bact., endocarditis
Groedel, Thompson[12]	1	During pneumonectomy
Missal, Crain[14]	1	Idiopathic
Levine[19]	1	Hypertension. Ischemia

* Simultaneous alternation of P waves.

heart rates; a group exhibiting intraventricular conduction disturbances; and a group exhibiting alternation of apparently normal complexes at normal or only moderately increased heart rates. It is the third type which is sometimes associated with pericardial effusion and with which we are concerned here.

Evidence that there is an association between alternation and pericardial effusion depends mainly on an analysis of all the electrocardiographic records of alternans of this type published with clinical data, available to us in the literature. Portions of the electrocardiograms of 26 cases were available for study. Of these, nine cases or one third are clearly associated with pericardial effusion, in a further two effusion seems likely (reference 4, cases 13 and 14), and in several others it cannot be excluded on the information supplied (table 1). The suggestion that there is an association between electrical alternans and effusion receives further support from Harvey and Whitehill[5] who in reviewing the electrocardiograms of 15 cases of tuberculous pericardial effusion remarked that "alternation in amplitude (of the ventricular complex) was occasionally observed as was change in the form of each second or third complex. These changes were usually present only in the cases with fairly large effusions". In an attempt to determine the frequency of electrical alternation in subjects with effusion, a series of 58 proven cases was reviewed. (Derived from the records of three Johannesburg hospitals together with cases seen personally by the authors.) Eight cases exhibited either permanent or transient alternation of the ventricular complex.

The conclusion that the alternans of pericardial effusion is unlike other types of alternans rests on several points. First, review of all the tracings of ventricular alternation which are available to us revealed simultaneous alternation of the P wave in three of our own cases and in six published records (table 1). In all but one[6] in which there were no data supplied there was an associated pericardial effusion. It is of interest that in only two[1, 16] of the instances cited in the literature had the P wave alternation been reported by the respective authors. To demonstrate this alternation it was sometimes necessary to enlarge these tracings from the size in which they had been printed, but when this was done the P wave alternation was usually clearly visible (fig. 1A and B). Though by no means proved, it seems possible that simultaneous alternation of auricular and ventricular complexes may be confined to cases of pericardial effusion.

Another unusual feature of these cases is the manner in which a regular alternans may

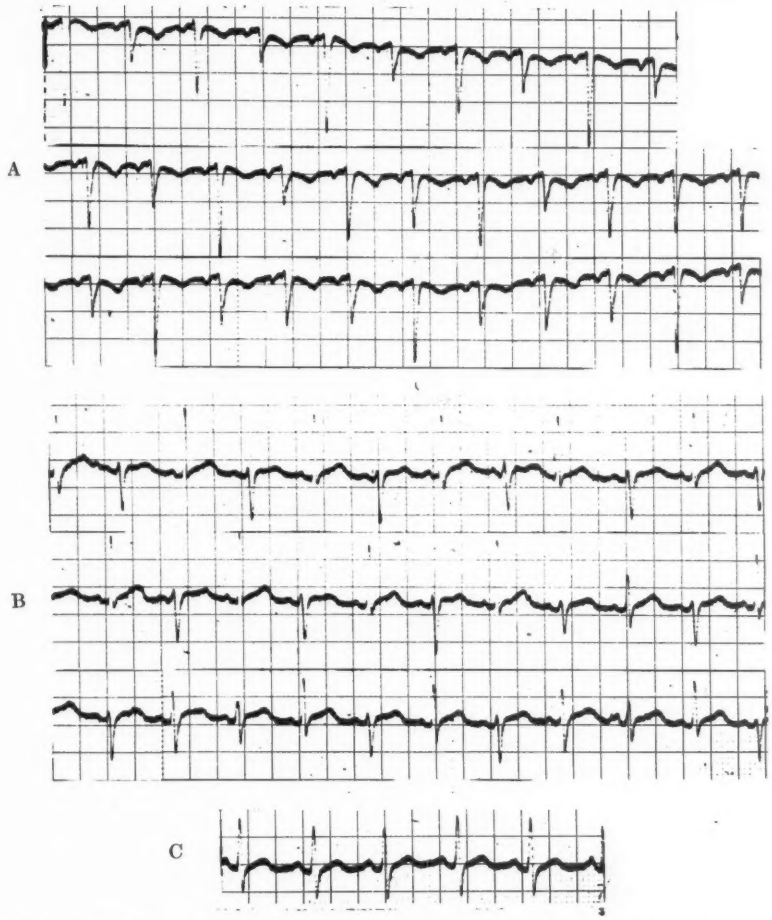

FIG. 2. A. Continuous tracing showing alternation merging into a more disorderly fluctuation of voltage. Respiration arrested. Lead CF_2. B. From same case as record in 2A. Continuous tracing showing alternation merging into an irregular fluctuation of voltage. Excluding the ninth beat which is premature and that which follows it, auricular alternation also is present until the last line of the record when an irregular fluctuation replaces it. Respiration arrested. Lead V_2. C. From same case as records in 2A and B. Record showing abolition of alternans immediately after aspiration of pericardial fluid.

change in a few beats to a fluctuation of voltage resembling marked respiratory variation as reported by Harvey and Whitehill.[5] In two of our cases, however, these changes were evident despite complete respiratory arrest. In one case (fig. 2) there are apparently two rhythms affecting the ventricular complex. One causes every second beat to be larger than its predecessor and the other causes every fourth beat to be especially large. In the other (fig. 1C) a slow waxing and waning of voltage is evident. There is insufficient evidence on which to decide whether these phenomena are unique to alternation associated with pericardial effusion. They are, however, a striking feature of some cases and we have observed nothing similar in records of alternation when not associated with effusion.

A third unusual feature of electrical alternans with pericardial effusion was the observation in

one case of alternation of heart sounds in the absence of alternation of the pulse. As the implications are of some importance the case will be discussed in some detail.

Case A. T., a female aged 42 years, had an infiltrative lung lesion and all the features of a large pericardial effusion with slight tamponade. The electrocardiogram showed a regular electrical alternans best seen in lead V_3 (fig. 3). This alternans frequently disappeared, but could always be reproduced by slight exercise such as rising once or twice to the sitting position. Once initiated it was unaffected by posture (supine, left lateral, sitting upright, sitting forward) or by respiration. Pulsus alternans could at no time be detected clinically or with a sphygmomanometer, but alternation of intensity of heart sounds could be easily heard with a stethoscope and was recorded phonocardiographically (fig. 4). Intra-arterial pressures were recorded during respiration and during voluntary apnoea (fig. 5), and although a well marked pulsus paradoxus was present during respiration, the tracing showed no fluctuation while breath was held. A supine ballistocardiogram was too disordered to be of much significance, but gave no evidence of mechanical alternans. An electrocardiogram recorded during paracentesis showed that the alternans disappeared after the removal of about 200 ml. of pericardial fluid and it has not been possible to reinduce it since.

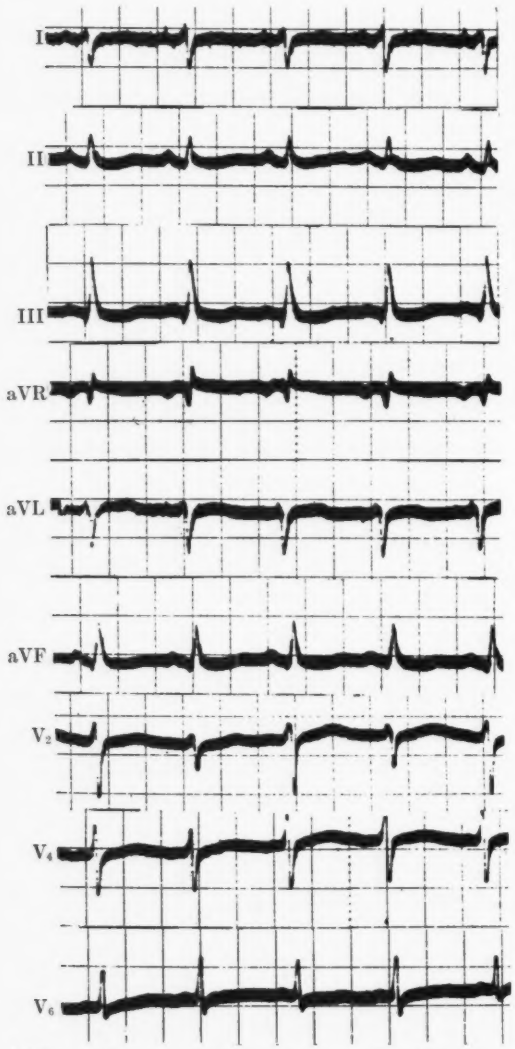

FIG. 3. Electrocardiogram of case A. T. Although not truly synchronous this record was made on a 2-channel electrocardiograph and has been mounted so that complexes correspond throughout. Respiration arrested.

It was concluded that, excluding isolated mechanical alternans of the right ventricle (a possibility which could not be tested in so ill a patient) movement of the heart relative to the stethoscope with alternate beats was the most likely explanation for the variation in heart sounds.

Discussion

Alternation of the ventricular complex is not a common phenomenon. Hamburger and coworkers[7] had seen only one example in a series of 10,000 electrocardiograms and Kalter and Schwartz[8] reported an incidence of 1 per 1,212 patients, though as these authors suggested it is probable that more cases will be found if careful scrutiny is made particularly of multiple chest leads. Although the number of tracings of alternans we were able to examine was small, the incidence of pericardial effusion in at least one third, and possibly more, must be considered significant. Neither alternans nor the respiratory-like fluctuations of voltage reported above have been seen by us in cases of pericarditis in the absence of effusion and it would appear that the effusion and the type of alternans under discussion must be etiologically connected. In addition the fact that these patterns were found on eight occasions in a review of electrocardiograms from 58 of our own cases of effusion indicates that they have obvious diagnostic value.

Isolated alternation of the auricular complex,

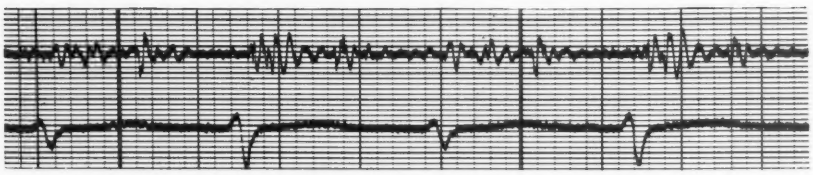

FIG. 4. Case A. T. Low frequency heart sound tracing above, with synchronous lead V_2 below. There is alternation of both the first and second heart sounds.

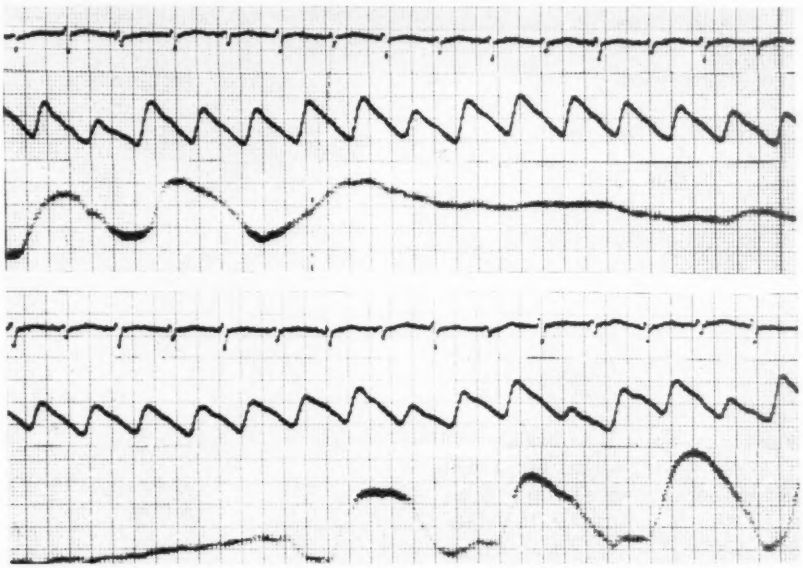

FIG. 5. Continuous recording of electrocardiographic lead V_2 (above), brachial arterial pressures (middle) and pneumogram (below). Note the complete absence of alternans best seen during apnoea.

though not uncommon in animal experiments,[9] is extremely rare in the human. We could find only one authentic example in the available literature.[10] Most authorities make no mention of it while an example shown by Katz[6] appears actually to be a case of alternate auricular premature beats. The occurrence of simultaneous alternation of auricular and ventricular complexes is a finding, therefore, which can hardly be fortuitous. Any hypothesis put forward to explain this association should also explain the fact that simultaneous alternation of auricular and ventricular complexes is an observation apparently confined to cases of pericardial effusion. It should also offer an explanation for the simultaneous alternation of the ventricular complexes and heart sounds in the absence of pulsus alternans observed in case A. T.

Previous theories of the mechanism of alternation could clearly not meet all these demands. The suggestion originally made by Baskind[3] that the phenomenon of electrical alternation in these cases might be the result of free movement of the heart in the pericardial sac would, however, be consistent with the observed facts.

On consideration it does not seem unlikely that the heart suspended in a large sac of fluid should move more than the normal organ. In view of the spiral arrangement of the great vessels as they leave the heart a periodic fluctuation in their tension might well produce a rotatory effect on the "floating" organ. The extent of movement would depend on the natural period of oscillation of the heart thus suspended, on its rate of contraction, and

possibly also on the presence of additional stimuli, such as respiration. In the majority of cases no apparent movement at all takes place. In others, however, a rotatory oscillation could be set up bearing a 1:2 relation with the heart beat which would remain fairly constant for long periods. In other cases a less regular oscillation might be set up bearing 1:2 or a 1:3 relationship with the heart beat. Respiration might well play a bigger part in the initiation of these slower movements, but as has been shown they may persist after respiration has been arrested.

Such an hypothesis would adequately explain the following observations:

(a) The obvious association between pericardial effusion and electrical alternans.

(b) The fluctuations in voltage other than true alternans found in some cases with pericardial effusion.

(c) Synchronous alternation of auricular and ventricular complexes, a result to be expected if the alternation were due to movement of the whole heart.

(d) Alternation of intensity of heart sounds in the absence of manometric or ballistocardiographic evidence of mechanical alternation. This, in terms of the present hypothesis would be the effect of cardiac movement bringing the heart valves closer to the chest wall with alternate beats.

Clearly this explanation of electrical alternans could apply only to cases of pericardial effusion. There remain those cases in which there is an obvious alternating disturbance of conduction, those cases associated with paroxysmal tachycardia and those cases without pericardial effusion which show electrical alternans at normal rates, with apparently normal conduction. In these cases the well known theoretical explanations are clearly tenable.[10, 11]

Summary and Conclusions

Evidence is produced that electrical alternans or a less regular fluctuation of voltage not due to respiration is sufficiently common to be of diagnostic value in pericardial effusion.

Simultaneous alternation of auricular and ventricular complexes has so far only been observed in cases with pericardial effusion and this association would appear to be unique.

It is suggested that the explanation for the fluctuations in voltage (regular or irregular) sometimes observed in cases of pericardial effusion is due to movement of the heart within the fluid filled pericardial sac, and some evidence is produced in support of this hypothesis.

Summario e Conclusiones in Interlingua

Es presentate datos demonstrante que alternantia electric (o voltofluctuationes minus regular) que non es causate per respiration occurre satis frequentemente pro esser de valor diagnostic in effusion pericardiac.

Alternation simultanee in le complexos auricular e ventricular ha usque nunc essite observate exclusivemente in casos con effusion pericardiac. Il pare que iste association es specific.

Nos submitte le these que le voltofluctuationes (tanto regular como etiam irregular) que se observa a vices in casos de effusion pericardiac es causate per le movimento del corde in le fluido intra le sacco pericardiac. Alicun datos que corrobora nostre these es presentate.

Acknowledgments

Our thanks are due to those physicians who have kindly allowed us to see their cases and to Professor G. A. Elliott and Doctor B. van Lingen for their assistance to us in writing this paper.

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Chronic Effusive Pericarditis

By S. Contro, M.D., G. De Giuli, M.D., and F. Ragazzini, M.D.

An unusual case of chronic pericarditis with effusion, lasting at least four years, in an asymptomatic child, is presented. The literature on the subject is reviewed. Attention is drawn to the fact that such cases exist, and should be considered when one is confronted with a case of cardiac enlargement of obscure etiology.

IT is generally believed that effusive pericarditis is an acute ailment. Well known textbooks of cardiology,[1, 2, 3] as well as the literature[4] on the subject, divide pericarditis into an acute and a chronic form, and consider the latter as synonymous with the various types of constrictive pericarditis. However, a survey of the literature reveals three cases[5, 6] in which the inflammation of the pericardium ran a chronic, quiet course with the presence of abundant fluid in the pericardial sac.

Recently, we had the opportunity to observe a case of chronic pericarditis with effusion of four years' duration in a child. The patient had no symptoms referable to the cardiovascular system, and the recognition of the cardiac lesion was made almost fortuitously. The purpose of this paper is to emphasize that pericarditis with effusion may assume a chronic course without evidence of constriction.

Case Report

A seven year-old girl of Italian extraction was first seen in January, 1949. Birth and development were normal, and there was no significant past medical history. Two days prior to being seen, she developed high fever, slightly productive cough, and dyspnea. At the time of examination the pertinent physical findings were: numerous crepitant rales at the left base posteriorly and cardiomegaly, with the left heart border percussed at the left anterior axillary line in the fifth intercostal space. There was no cyanosis, cardiac murmurs, or signs of congestive failure. A diagnosis of left lower lobe pneumonia was made, and the patient was placed on penicillin therapy and bed rest in her home. After three days of this regimen, the temperature returned to normal, and the rales in the left lung disappeared. Six days later, when she was again ambulatory, x-ray films of the chest were taken, which revealed clear lung fields with sharply defined costophrenic angles and no evidence of fluid in the pleural cavities (fig. 1; a, b, c). The vascular markings were within normal limits, and the aortic contour appeared normal. There was generalized enlargement of the heart, most marked to the left. An electrocardiogram (fig. 2) taken at this time showed low voltage in the limb leads, but otherwise was within normal limits. Due to lack of symptoms and physical findings, a diagnosis was deferred, and it was decided that the patient should be observed at regular intervals to determine the evolution of the above-noted cardiac abnormality.

The patient was next seen for routine examination 10 months later. At this time she was asymptomatic, and there had been no change in the physical findings or x-ray picture.

Due to her sense of well-being and complete lack of symptomatology, she was not seen again until October, 1952, almost four years after the onset of the illness. During this period she had contracted measles which had been treated by another physician with apparent complete recovery. At this time a chest x-ray film again revealed normal lung fields, and generalized cardiac enlargement. There had been no change from films taken three years previously. Fluoroscopy showed diffuse cardiac enlargement with feeble cardiac pulsations. A roentgenkymogram (fig. 3) confirmed the impression of minimal pulsations along the heart borders.

In December, 1952, following an upper respiratory infection, the patient developed high fever, cough, and dyspnea. There was slight dullness to percussion with bronchial breathing and inspiratory rales at the left base posteriorly. Further physical examination at this time revealed no other abnormality except the previously reported cardiomegaly. A diagnosis of left lower lobe pneumonia was again made, the patient was hospitalized, and therapy with penicillin and streptomycin was instituted.

The laboratory findings at this time were as follows: The blood count showed 4,320,000 red blood cells and 13,000 white blood cells per cubic millimeter and hemoglobin of 80 per cent. Di-

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A B C

FIG. 1 A, B, C. Roentgenograms of the chest in the frontal, left and right oblique projections. See text.

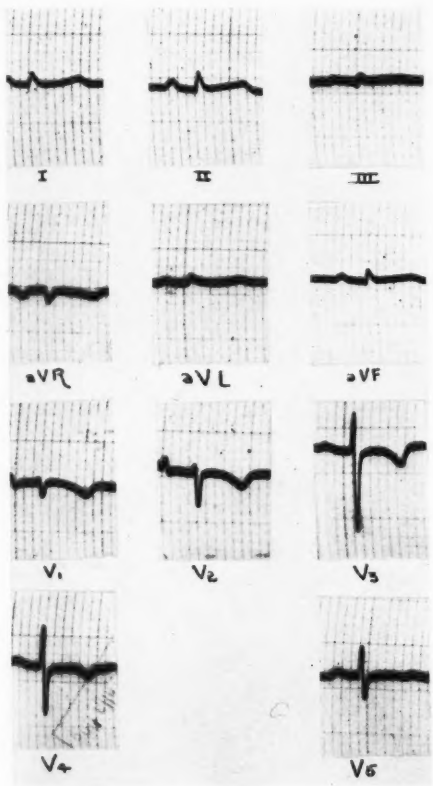


FIG. 2. Electrocardiogram. See text.

erential count showed polymorphonuclear leukocytes 64 per cent; lymphocytes 34 per cent; osinophiles 1 per cent; mononuclear cells 1 per ent. Urinalysis was normal, with constant absence f ketone bodies on fasting samples. Fasting blood ugar was 100 mg. per 100 cc. Blood sugar rose

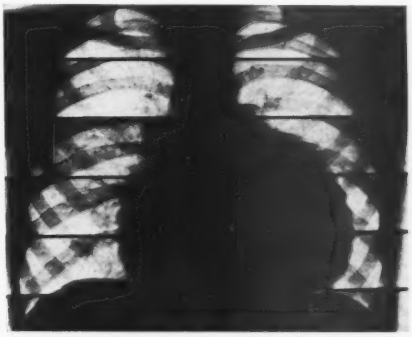


FIG. 3. Roentgenkymogram in the frontal projection showing minimal pulsations of both cardiac borders.

normally after injection of epinephrine. Blood urea nitrogen was 18 mg. per 100 cc. Total serum cholesterol was 180 mg. per 100 cc. The basal metabolic rate was plus 10. The Wasserman test was negative. The test for lupus erythematosus was negative on two occasions. Agglutinations for typhoid, paratyphoid, and brucella were negative. The Congo red test was normal. Skin test and complement fixation for echinococcus was negative. The result of a Mantoux test was 1 plus at 24 hours; 2 plus at 48 hours.

The patient's symptomatology gradually diminished. Over a seven-day period, the temperature returned to normal: physical findings in the lungs disappeared; and the white blood cell count dropped to 7,000. At this time it was decided that further x-ray studies were indicated.

Artificial pneumomediastinum was induced to rule out the presence of an extracardiac mass. Films (fig. 4) taken at this time revealed the thymus to be normally located in the anterior mediastinum and to be of normal size. No extracardiac mass was demonstrable.

An angiocardiographic examination was then performed. Films (fig. 5 a, b) revealed the cardiac chambers to be centrally located and apparently of normal size. However, the distance from the inner walls of the right and left chambers to the outer limits of the cardiac shadow measured about 3 cm.

Because these findings were considered characteristic of pericardial effusion, a pericardiocentesis was performed, and 70 cc. of clear, light-yellow fluid was aspirated. This did not clot on standing and contained 5 Gm. of protein per 100 cc. The fluid was centrifuged and microscopic examination revealed the presence of 10 to 15 lymphocytes per high power field. Gram, methylene blue, and Ziehl-Nielsen stains failed to reveal any organisms. Guinea pig inoculations and culture for acid-fast bacilli were negative.

FIG. 4. Pneumomediastinum in the lateral projection. A thymus of normal size is outlined in the anterior upper mediastinum.

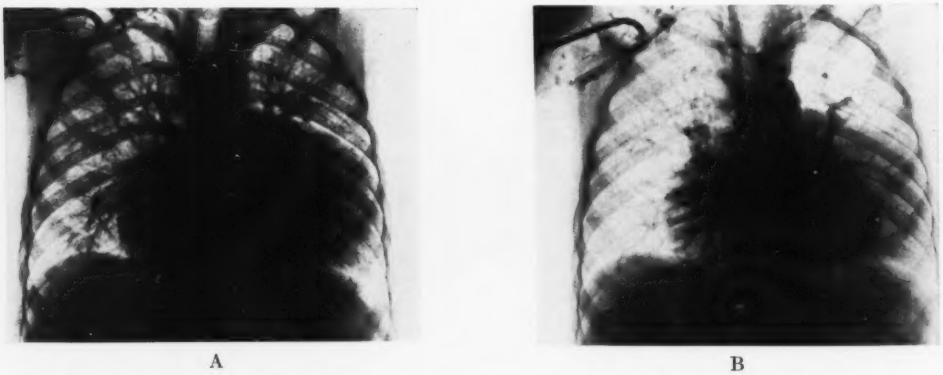
At the time of pericardiocentesis, air was injected into the pericardial sac and was seen to move freely within an enlarged pericardial cavity at fluoroscopic examination. Moreover, the patient was rotated through 360 degrees in the horizontal plane and through 180 degrees in the vertical plane (so that the feet were in the upright position). In the latter position, the cardiac apex was outlined by air. Films were taken in upright and left lateral decubitus positions (fig. 6 a, b) and confirmed the fluoroscopic findings of an air-fluid level, normal inner cardiac silhouette, thin outer pericardial margin, and absence of loculation of fluid.

The patient was placed on streptomycin and isoniazid therapy with no change in the physical findings. She remained asymptomatic and there was no further change when last seen in June, 1953.

DISCUSSION

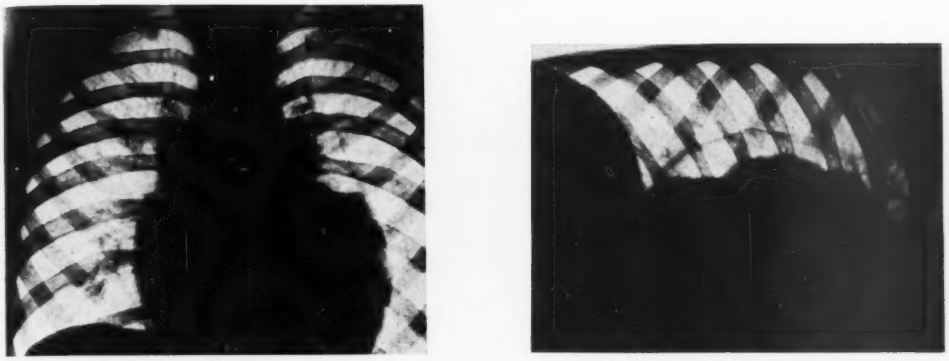
The diagnosis of effusive pericarditis was not initially entertained in the above case, owing to the belief that this condition always runs an acute course. The presence of a normal development and normal tolerance for exercise, as well as the absence of auscultatory findings, first drew our attention to the differential diagnosis of enlargement of the cardiac shadow.

The unlikely possibility of an extracardiac mass embracing the entire cardiac contour and simulating cardiac enlargement was excluded by the pneumomediastinum studies. The lack of symptoms and of progressive findings ex-



A B

FIG. 5. Angiocardiogram in the frontal plane (A, 3 seconds after the injection, B, 6 seconds after the injection) showing no chamber abnormality. For further explanation see text.



A B

FIG. 6 A, B. Pneumopericardium in frontal upright and left lateral decubitus positions.

cluded the various forms of myocarditis and of tumors of the myocardium.

Tumors of the pericardium might have been considered. Jucker,[7] in 1941, published two cases of primary pericardial tumor and reviewed the 22 cases previously reported. The author concluded that they can be divided into two main groups: those which produce hemorrhagic pericarditis, and those which produce infiltration of the pericardium. In both groups the symptomatology is rapidly progressive, making this an unlikely possibility in the present case. The diagnosis of chronic effusion due to myxedema was untenable in view of the normal appearance of the patient and the negative laboratory results.

A cardiac form of Von Gierke's disease was considered. The absence of ketone bodies in fasting urine and a normal rise of blood sugar after injection of epinephrine militated against it. Moreover, the survival of a patient, with this condition for four years without symptoms has never been reported. Di Sant' Agnese and coworkers,[8] in a recent article, reviewed all the cases on record and showed that these patients are severely incapacitated and do not reach one year of age.

The laboratory studies also made unlikely such causes of cardiac enlargement as primary amyloidosis and echinococcosis.

The angiocardiogram was typical of pericardial effusion. A diverticulum of the pericardium was excluded by pneumopericardium.

In seeking the etiology of the effusion, the remaining possibility which can be considered seriously is tuberculosis. In favor of the diagnosis of tuberculous pericarditis is the positive Mantoux test. However, more than 50 per cent of the population in the patient's community are Mantoux positive, and, therefore, the positive reaction may have been a coincidental finding. Culture for *Mycobacterium tuberculosis* and guinea pig inoculations were negative and the patient showed absolutely no response to two and one-half months of antituberculous chemotherapy in adequate dosage. Furthermore, the patient was completely free of symptoms and the pneumopericardium showed no thickening of the parietal pericardium. In the absence of an anatomical examination, tuberculosis as the etiological factor in this case cannot be completely excluded. However, for the reasons cited above we believe this to be unlikely.

A search of the literature has revealed very few reports of long-standing pericardial effusion. Blumenfeld's case[5] followed massive irradiation for a carcinoma of the breast and lasted about four years. Autopsy revealed remarkable fibrous thickening of the pericardium with no specific inflammatory reaction. The remaining two cases are reported in the article published by Barker and Johnston in 1950.[6] Along with another case of doubtful chronicity, these cases, on microscopic examination of the pericardium, revealed only nonspecific changes. These cases are exceptions to the oft-quoted statement that the diagnosis of tuberculous

pericarditis should be made when no other etiology can be established.

The possibility of a congenital lesion in our case has to be considered since the lesion was first discovered at the age of 7 years. This might take the form of a congenital obstruction to the lymphatic drainage of the pericardium. The protein concentration of 5 Gm. per 100 cc. in the pericardial fluid would fit this hypothesis. However, no such case has ever been recorded and, without anatomical evidence, this idea can remain only speculative.

Summary

A case of chronic, symptomless pericardial effusion in a child is presented. Despite adequate search, no etiological factor was discovered. A survey of the literature reveals only two or three comparable cases.

Attention is drawn to the possibility of the existence of a definite syndrome of chronic pericardial effusion.

Summario in Interlingua

Es presentate un caso inusual de chronic pericarditis effusive in un puera asymptotic observate durante quatro annos ab le septime al dece-prime anno de su etate. Un revista del litteratura revelava solmente duo o tres casos comparabile. Nonobstante, le occurrentia de tal casos es establite e debe esser prendite in consideration quando on se trova confrontate con un allargamento cardiac sin etiologia clar.

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On Cardiovascular Sound

Further Observations by Means of Spectral Phonocardiography

By VICTOR A. MCKUSICK, M.D., GEORGE N. WEBB, M.S., J. O'NEAL HUMPHRIES, A. B. AND JAMES A. REID, B.S.

Spectral phonocardiography, an adaptation of the method of sound spectrography devised at the Bell Telephone Laboratories, differs from conventional oscillographic phonocardiography principally in the fact that frequency spectrum is displayed as well as the dimensions of time and intensity. The display of frequency spectrum is responsible for three advantages of the method: (1) Quality, or timbre, is given physical definition, (2) resolution in the time dimension is improved, and a (3) a better display of the wide dynamic range of cardiovascular sound is attained. This method can do, or can be made to do, all the ear can, and can probably emulate the performance of the ear because 1) it is not wed to a particular frequency-intensity response curve, 2) it suffers from no "psychoacoustic" impediments, 3) it provides better resolution in the time dimension, and 4) it produces permanent, quantifiable records. Discussed here are selected features of mitral valve disease, aortic valve disease, gallops, systolic clicks, and extracardiac sounds. In general, intensity and peak frequency (or frequency range) vary in a parallel manner in sound of cardiovascular origin. Artefacts due to noncardiovascular ambient noise and to electrical interference can be identified and disregarded in the heart sound analysis.

CONVENTIONAL phonocardiography, now about 60 years old,[1, 2] has contributed significantly to the interpretation of clinical stethoscopy of the cardiovascular system and to the understanding of cardiovascular physiology, normal and abnormal. Timing of auscultatory findings and temporal correlation with other physiologic events have been the principal types of usefulness in both the clinical and the physiologic domain. Particularly at the lower end of the frequency scale where the ear is much less sensitive the conventional phonocardiogram has provided valuable information. Inevitably the information about cardiovascular vibrations in the audible range is limited by the methods available to the investigator. Further advances in the study of heart sounds and murmurs require new methodological approaches. This communication presents observations made by one such new method, sound spectrography, which in its application to the study of cardiovascular sound may well be termed spectral phonocardiography. This report is a continuation of two early ones, one of which was largely technical[3] and the other more particularly clinical.[4]

About 10 years ago the Bell Telephone Laboratories developed a method for three dimensional display and analysis of speech sound.[5] It has been called sound spectrography (also "visible speech") because frequency spectrum is displayed in detail. It was early demonstrated that whereas the oscillogram of speech sound has no particularly distinctive characteristics—it might, in fact, represent a very abnormal phonocardiogram—the spectrogram of the same sound is sufficiently detailed and characteristic that one can not only learn to read what is being said but also discern minor individual peculiarities of speech such as regional accents. The application of this method to phonocardiography was further encouraged by verbal reports of success with its use in other connections: for example, when used on complex airplane engines it has

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been possible to detect and diagnose abnormality much as a good mechanic does in listening to an automobile motor.

Elsewhere[3] we have described the modifications of the commercially available sound spectrograph which are necessary for the particularly demanding application of phonocardiography. These modifications are of three main types:

(1) The filter system must be modified to make available the width of pass-band which provides optimum simultaneous resolution in the time and frequency dimensions.

(2) Parallel recording of other physiologic events (for correlative purposes) has been instrumented.

(3) Improved resolution of the intensity display has been obtained by development of a photographic recording system.

Methods

Figure 1 presents a schematic representation of the methods employed in these studies. For pick-up from the patient, a condenser-type microphone (Altec 21BR150) has been employed. This is a calibrated transducer with linear characteristics. Recordings were made under as quiet ambient conditions as possible. The microphone-chest piece combination employed provides a maximum of 20 decibels attenuation of ambient noise above 200 cycles per second. The patient is essentially isolated from floor vibrations by an air mattress.

An Ampex two-channel, type 350, magnetic tape recorder has been employed. Recordings have been made at 7½ inches per second. To record the full dynamic range of the heart sounds, three degrees of low frequency compression have been available. With no compression the response characteristics of the entire system are flat above 30 cycles. At 20 cycles the response has dropped 5 to 10 decibels and at 15 cycles has dropped a maximum of 20 decibels below the response level above 30 cycles. Initial recording on magnetic tape has increased the flexibility of the method. At the convenience of the investigator, the tapes can be edited and sections selected for analysis. Recording at the bedside, in the operating theatre, or in the animal experimental laboratory has been feasible.

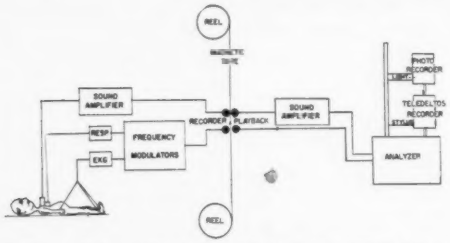

Fig. 1. Schematic representation of spectral phonocardiography. The heart sounds are first recorded on magnetic tape. Electrocardiogram, respirations and other physiological events are recorded simultaneously, being put on the tape by means of frequency-modulated carriers. The tapes are edited and sections selected for analysis. Simultaneous direct-written (below) and photographic (above) recordings can be made. See text for further description of analyzer.

By means of frequency-modulated carriers, electrocardiogram, respiration mark and other physiologic events have been recorded simultaneously on the magnetic tape and then on the spectral phonocardiogram, as indicated in the sketch (fig. 1). The conventional phonocardiogram can, if desired, be included as one of these parallel recordings.

In effect the principle of the analyzer of the spectral phonocardiograph is this: the segment of sound for analysis is "played over" from the original tape to the magnetic margin of a disk mounted on the same axis as the kymograph drum on which the records are made. The analyzer itself is in essence a single pass-band filter the tuning of which is changed progressively as the segment of sound being analyzed is played back repeatedly through it. For example, during the first rotation of the magnetic disk and the coaxial drum, the information in the 15 to 20 cycle per second band is inscribed on the record, with the second rotation the information in the 20 to 25 cycle per second band and so on up the record from bottom to top until the entire frequency scale has been scanned.

Note that in the finished record three variables of the heart sounds are displayed. As usual, time is on the abscissa. Frequency spectrum is on the ordinate. Intensity is indicated by degree of blackness of any given portion of the record since the brilliance of the light in the photographic recording unit (above in fig. 1) is a function of the intensity in each frequency band and since there is also intensity-modulation of the spark of the direct-writing unit (below in fig. 1). Most of the recordings up to this time have been made on electrosensitive paper, i.e., are of the direct-written type. Since the range of intensity displayed by this paper is limited, perhaps to 15 decibels, the photographic recording system has been devised to increase the resolution in the intensity dimension by several times. Although the dynamic range of the heart sounds may be as much as 100 decibels, the range in any one frequency band should be much less and easily encompassed by the capacities of the display unit. More of a problem is the limitation of intensity recording imposed by the two magnetic recording steps. A comparison of a direct-written and a photographic recording is provided in figure 2.

In the analyzing step the pass-band which has

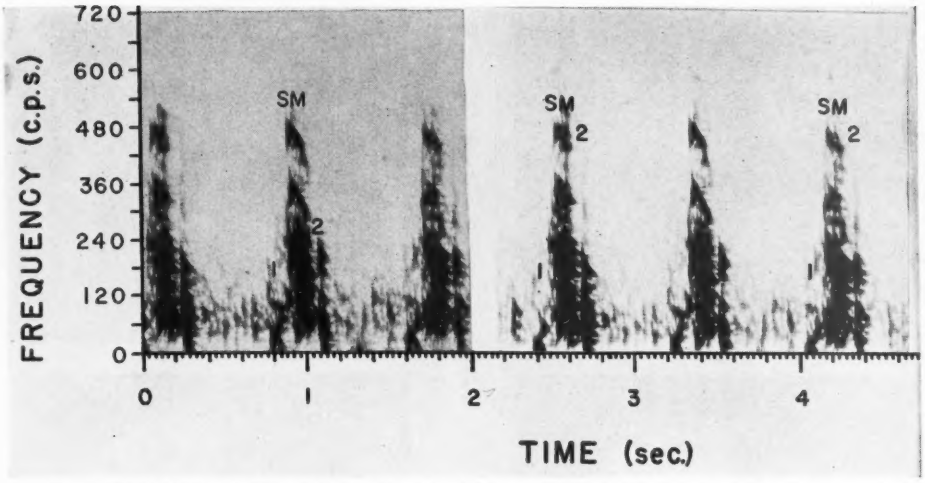

FIG. 2. On the left, a direct-written and on the right, a photographic recording of a rasping, musical systolic murmur of aortic stenosis. Records made simultaneously.

provided optimum simultaneous resolution in frequency and time has been one with a width of about 23 cycles per second at 6 decibels[3] below the intensity level at the center frequency. However, occasionally when the information desired was of a special variety other widths of pass-band might be employed, e.g., a wider one for particularly sharp time definition. A 750 cycles per second frequency range was adequate in the majority of cases although a 1500 cycles per second or higher scale was occasionally necessary to encompass the total frequency range encountered. *In essence*, then, since the drum rotates 425 times in the inscription of the analysis from 0 to 750 cycles per second, we have analyzed these sounds through the equivalent of approximately 425 overlapping filters, each with its center frequency about 1.8 cycles per second from the next.

The presently used spectrograph produces a record with a four-inch frequency scale (ordinate). A segment of sounds 6.6 seconds in duration is displayed on a record 12½ inches long.

Calibration of intensity has been accomplished by the introduction just beyond the microphone of a calibrating signal at 60 cycles. By means of the cathode ray oscillographic monitor, identical gain in the step of "playing over" into the analyzer is assured. We have adopted the practice of noting in connection with each finished record the oscillographic amplitude of the calibrating signal in millimeters. The microphone has been held to the chest in such a way that pressure with which it is applied is the weight of the microphone itself (fig.). This obviates the sound variations which result when a rubber strap or similar nonstandard device is employed. It is possible by these means to obtain

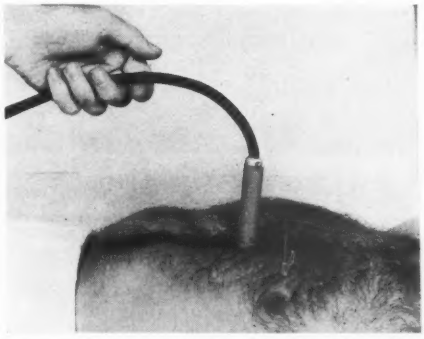

FIG. 3. The pressure of application of the microphone is standardized; it is the weight of the microphone.

recordings which, as far as the sound which arrives at the surface of the chest is concerned, are entirely comparable from time to time in the course of valvular heart disease, before and after operation, and so on.

It may appear that this method has sacrificed precise intensity definition for frequency detail. It should be noted, however, that intensity has most significance in relation to the frequency level at which it is located. Further detail as to intensity at specific points in time is provided by the intensity-frequency "sectioner" of the sound spectrograph.[3, 4] Such "sections" allow one to state, if such detailed information be of use in specific situations, the maximum intensity (in dynes per square centimeter of sound pressure or other unit) in a given frequency band at a given point in time.

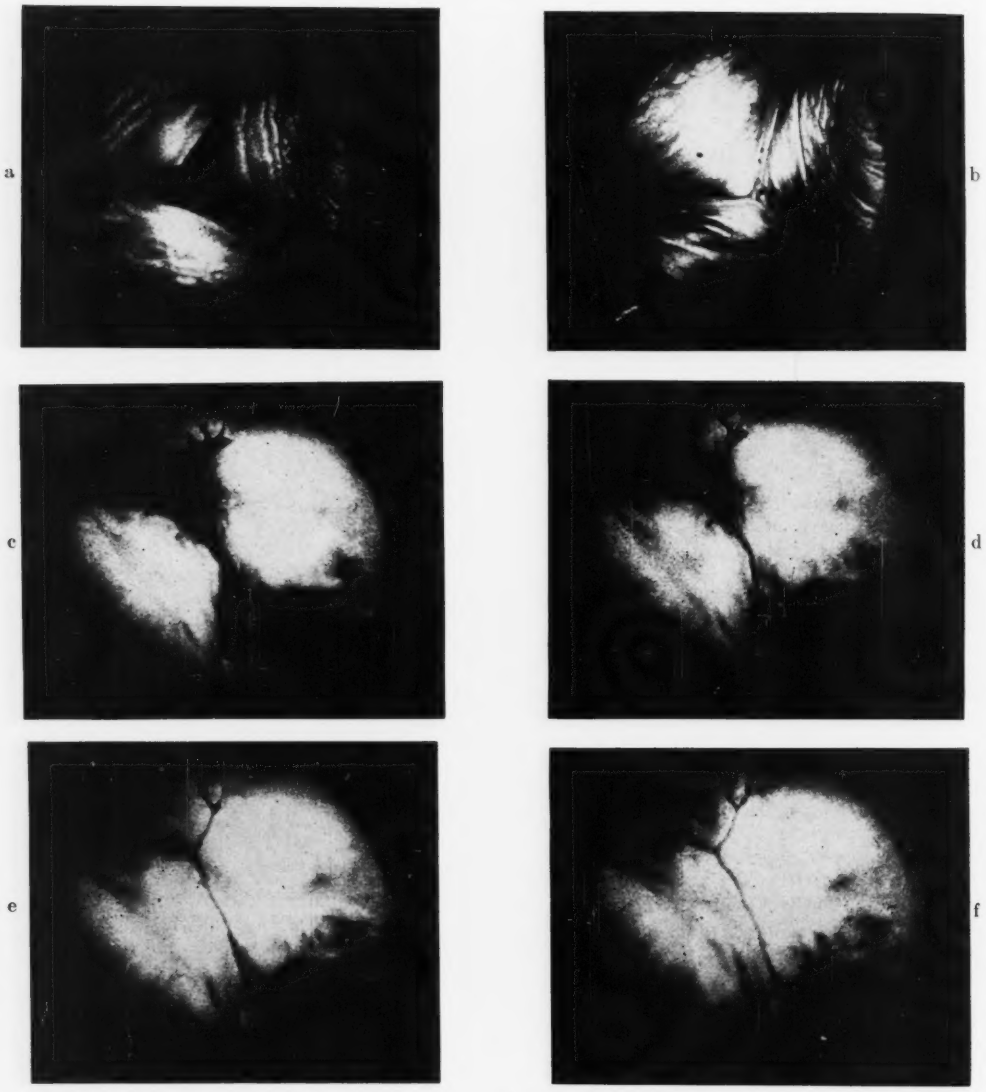

FIG. 4, a–f. In "a" and "b" are presented successive frames in the closure of the pulmonary valve; in "c" to "f" are presented a comparable series in the closure of the tricuspid valve. See text for details.

SOME ASPECTS OF NORMAL HEART SOUNDS

The first heart sound is often a longer sound than the second heart sound.[5] Figure 4 presents two sequential frames (made at the speed of 24 frames per second) in the closing of the pulmonic valve and four in the closure of the tricuspid valve in the same isolated beef heart under identical circumstances.* It is of interest that the tricuspid valve took about twice as long to close. The fact that the tricuspid valve closed first at the middle is also of some interest. Lamb[6] states that "according to a general

* From a film (PMF5162) made by the Armed Forces Institute of Pathology.

principle . . . the higher harmonics are excited in greater relative intensity the more abrupt the character of the originating disturbance." This principle may explain in part the higher frequency content of the second sound as compared with the first and also the high frequency content of systolic clicks, opening mitral snaps and the valve sounds in the fetus, children, tachycardia and small animals.

Diseases of the Mitral Valve

Few sounds commonly encountered in clinical practice are more complex in their genesis and acoustics than those associated with mitral stenosis. It is useful in this connection to refer to Duroziez's onomatopoetic device: "fout-ta-ta-rou." [7] "Fout" refers to the presystolic murmur and snapping first mitral sound; "ta-ta", to the second sound and the opening snap; "rou" to the so-called mid-diastolic component of the diastolic murmur, which may be introduced by a discernible third heart sound. (See fig. 5.)

There are two principal theories of the genesis of the opening snap: one holds that it is due to sudden checking of opening.[8] The other holds that the opening snap of the mitral valve and perhaps the snapping first sound at the apex, the closing mitral snap if you will, are the result of a "wind-in-the-sail" mechanism. Obviously the theories are not mutually exclusive.

Shown in figure 6 is a sketch which serves to illustrate the second theory. It is generally held that the type of mitral stenosis likely to produce an opening mitral snap is that in which the valve leaflets are fused into a funnel-shaped curtain with ring-like thickening of the

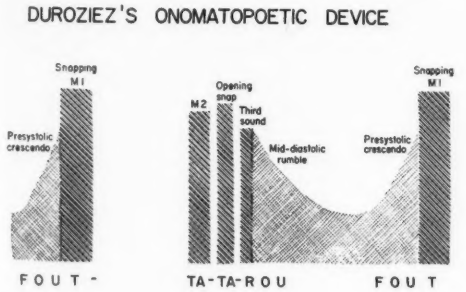

Fig. 5

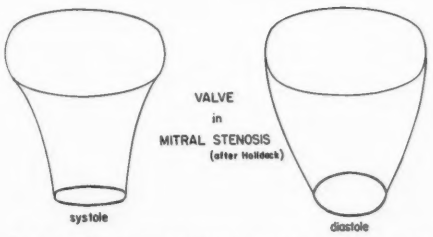

Fig. 6. The abrupt billowing of the mitral curtain toward the atrium with ventricular systole and toward the ventricle in diastole is a possible explanation for the snapping first sound and the mitral opening snap in mitral stenosis. Adapted from Holldack (9).

margin of the "fishmouth" and some increased rigidity of the valve curtain, yet sufficient flexibility to permit a snapping back and forth as pressure relationships on its opposite surfaces undergo cyclical variations. With fall in ventricular pressure below that of the left atrium the valve curtain billows toward the ventricle producing a snapping sound, "the opening snap." With ventricular contraction and elevation of ventricular pressure above that in the atrium an abrupt bulging occurs in the opposite direction with production of a snapping sound which is probably responsible in part for the accentuated first apical sound. Holldack[9] has aptly compared the opening snap to the snapping of a sail with shift in the wind. It was the opening snap which in combination with the first and second sounds produced at least one type of *bruit de rappel* described by Bouillaud[10] who with others was also responsible for relating this type of heart involvement to acute inflammatory rheumatism (rheumatic fever). Rouches[11] introduced the customarily used term *le claquement d'ouverture de la mitrale*, saying his mentor Potain used it in his lectures. William Sidney Thayer[12] introduced the English analogue: "opening snap." The study of Margolies and Wolferth[8] published in 1932 remains one of the best. It seemingly received scant notice at the time it appeared, probably because of limited interest in, and restricted value of, the auscultatory minutiae of valvular lesions. These investigators described the variation in the second sound-snap interval with heart rate, the not infrequent gap between the snap and

the beginning of the rumble and the area of maximum audibility in the left midprecordium.

The opening snap has, in most cases, persisted after operation. The "wind-in-the-sail" explanation is not entirely satisfactory in this instance; the postoperative opening snap may be a less specific type of flapping of the stiffened leaflets—like a housewife shaking a rug or a bed-sheet. Or the persistence of the opening snap may be evidence for the view that abrupt checking of opening is principally responsible for its genesis.

The opening snap is usually loudest in an area of the chest directly overlying the mitral orifice. The scatter map of the points of maximum audibility in the series of Margolies and Wolferth resembles the fluoroscopic image in a case of mitral stenosis with valvular calcification. The opening snap is often louder in the pulmonary area rather than at the apex. It is to be noted that although the second pulmonic sound may be genuinely split in mitral stenosis, more often what has in the past been called a split or reduplicated second pulmonic sound is in fact the second pulmonic sound proper plus the opening mitral "snap." Not infrequently the opening snap is louder in the aortic than in the pulmonary area. Wood[13] found that the opening snap was absent in a case of predominant mitral stenosis with aortic regurgitation. He suggested that the regurgitation against the aortic leaflet of the mitral valve during isometric relaxation and early diastole might prevent the sudden billowing of the mitral sail responsible for the snap. Gallavardin[14] in one case and Mozer and Duchosal[15] in two likewise failed to detect an opening snap in the presence of aortic regurgitation. On the other hand, Margolies and Wolferth[8] found five cases of opening snap in spite of the presence of aortic regurgitation.

Within limits the interval between the second sound and the opening snap tends to vary directly with the duration of the preceding diastolic period. Since this interval is a measure of isometric relaxation, the question of the basis for this variation resolves itself into the question of why isometric relaxation is shorter after shorter diastolic periods, and vice versa.

Opening snaps are identified as such by several means: (1) They tend to be 0.08 to 0.10 second after the second sound. (Split heart sounds, in the absence of bundle branch block or shunt with discrepancy in the stroke volumes of the two ventricles, seldom show a separation of the components of more than 0.06 second. A third heart sound gallop seldom is closer than 0.12 second to the second sound.) (2) In the spectral phonocardiogram in particular it is usually possible in some areas to demonstrate slight splitting of the second sound proper, thereby accounting for the closure of both sets of arterial valves. (If the usually employed filter setup is changed for one with wider pass-band characteristics[4] the splitting can be better displayed.) (3) They are snapping or clicking in quality as evidenced in the spectrogram by relatively high frequency span and often either harmonic pattern or relatively pure frequency content.

Somewhat puzzling is the brief interval which is present in many cases between the opening snap and the onset of the murmur. (In others the rumble begins immediately with the opening snap.) Can it be that the pressure differential adequate to snap the mitral curtain toward the ventricle is not sufficient to spread the stenotic fishmouth and initiate passage of blood to the ventricle (and the murmur)? Is the anatomical difference between the cases with an interval and those without a qualitative or a quantitative one? In general it appears that the difference is quantitative, i.e., that the cases, in which the rumble begins immediately with the opening snap, have a higher grade of mitral obstruction.

It is also difficult to understand the origin of a third heart sound in this situation where filling of the ventricle is impeded. It seems likely that the third heart sound recorded in some cases of "tight" mitral stenosis is a third sound gallop arising in the right ventricle. With exercise and the left lateral decubitus position the third sound may be exaggerated and the opening "snap" diminished. If a third sound gallop appears to arise in the left ventricle, as, for instance, in cases of mitral stenosis without signs of right ventricular hypertrophy and dilatation and therefore without basis for a right ventricular origin of the gallop, insignifi-

ant mitral valve obstruction is likely to be present.

The genesis of the snapping first sound may be in part that indicated by the sketch in figure 6 and in part snapping of the shortened, stiffened chordae tendineae when they bring the attached mitral valve "up short" on contraction of the ventricle. Furthermore, the fibrotic change in the valve cusps may be responsible for part of the ringing quality just as similar changes in the aortic cusps in rheumatism and perhaps in syphilitic aortitis may produce a ringing, accentuated second aortic sound. There is a close correlation between an accentuated ringing first apical sound and an opening mitral snap; both, furthermore, are indicative of predominant mitral stenosis.[13]

As is discussed and demonstrated below (see figs. 13 and 15) the characteristic murmur of ejection stenosis (e.g., aortic or pulmonary stenosis) is diamond-shaped on conventional phonocardiography and like a Christmas tree in the spectrogram. These configurations are mainly due to a midsystolic peak in intensity and in frequency. In mitral stenosis one might anticipate that the presystolic murmur would have a similar configuration. Such is probably the case when the P-R interval (atrioventricular conduction) is sufficiently prolonged that the presystolic murmur "stands alone" and is not cut short by the first heart sound. The presystolic crescendo can be considered to represent half the "Christmas tree" of an ejection stenosis murmur.

Conventional phonocardiography has not always corroborated the auditory impression of a crescendo character of the presystolic murmur of mitral stenosis. The reason in many cases may have been that the instruments used were insufficiently sensitive to the higher frequencies (which impress the ear most) to demonstrate the intensity increment which the higher pitched components contribute to the presystolic crescendo.

Note in figure 7, a recording from the apical area (D. C., 687240), the close reproduction of the Duroziez device. In the pulmonary area (not displayed) both a split second sound and an opening mitral snap were evident. In some cycles a distinct third heart sound is seen. The half Christmas tree appearance of the presystolic murmur is well displayed.

The patient (S. O. N., 616116) from whose apical area the recordings in figure 8 were made at an interval of six months has a type of diastolic rumble which begins immediately with the opening snap. In the interval between the two recordings the patient developed atrial fibrillation. Note the disappearance of the presystolic element of the diastolic rumble and the variation in the interval between the second sound and opening snap. In the first recording the interval is brief since the heart

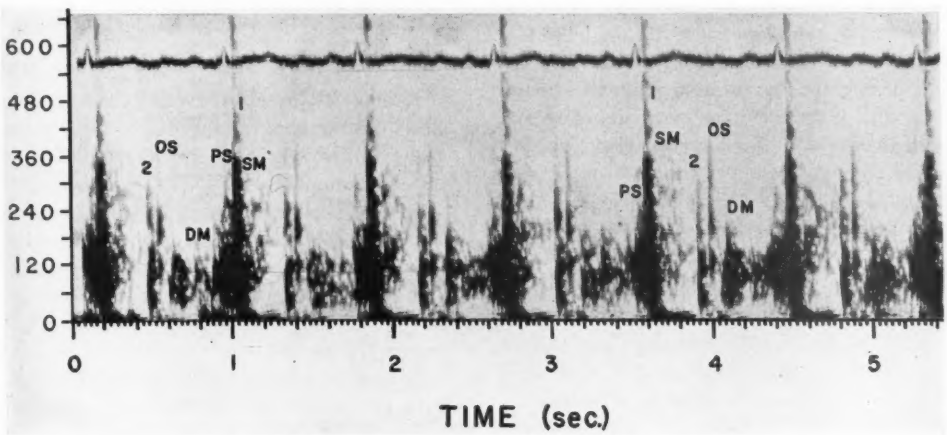

FIG. 7. Apical area in patient with predominant mitral stenosis

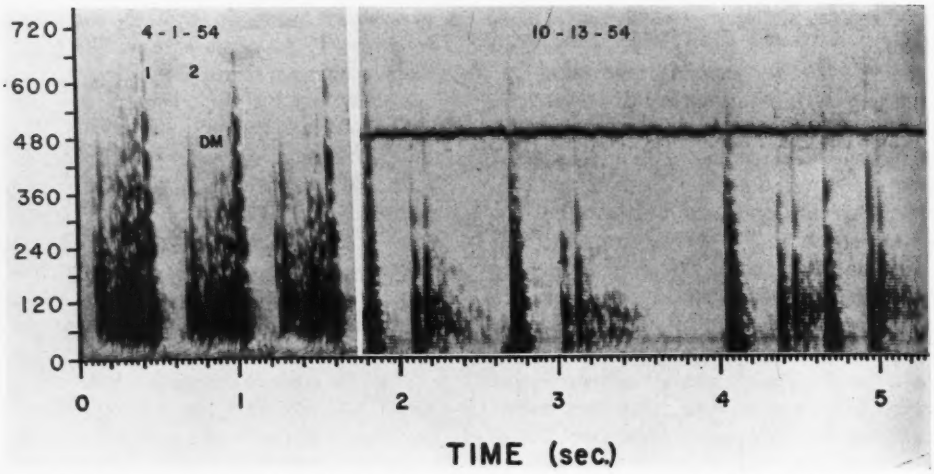

FIG. 8. Recordings from the apical area before and after the development of atrial fibrillation.

rate is rapid with correspondingly short diastolic periods. With atrial fibrillation the interval is shorter after the shorter diastolic periods, e.g., the last cardiac cycle in the recording. Variation in the length of isometric relaxation is indicated by the variation in the position of opening snap in relation to the second sound. The second sound is relatively constant in its position relative to the QRS of the electrocardiogram. The delay of the first heart sound in the presence of mitral stenosis and atrial fibrillation[16] is displayed by the recording. Usually in atrial fibrillation the first heart sound is accentuated after shorter diastolic intervals because the atrioventricular cusps come together from a more widely open position. In this case of mitral stenosis, an opposing factor, namely, poor ventricular filling with short diastoles, may dominate and result in a diminution of both the intensity and the frequency span of the first sound. (See the first sound in the last cycle of fig. 8).

Figure 9 presents the recordings from the pulmonary area and apex of a patient (H. L., 346674) with virtually all the hallmarks of mitral stenosis *except* an unequivocal and consistently present diastolic rumble. We have observed this situation previously and it is rather commonplace after mitral valvulotomy. In this pair of recordings note that the opening snap is much more striking at the pulmonary

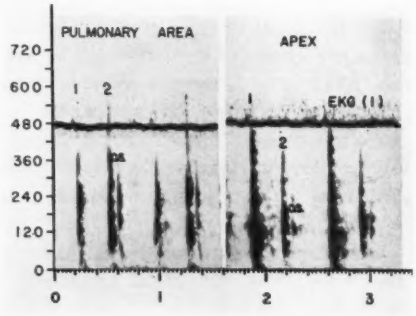

FIG. 9. Recorded at areas indicated in case with all hallmarks of mitral stenosis except unequivocal rumble. Note broad, notched P wave of electrocardiogram; opening snap louder in pulmonary area; apical first sound ("1") accentuated in both intensity and peak frequency.

area than at the apex. Note, furthermore, the accentuated and ringing (viz., the harmonic pattern) first apical sound and the accentuated second pulmonic sound. That the extra sound is indeed an opening snap and not the second component of a widely split second sound is supported by the fact that slight splitting of the second sound is present accounting for both the aortic and the pulmonic closure sounds.

Figure 10 presents the sounds at the apex in a patient (A. B., 167680) who three years previously had mitral valvulotomy for relatively pure mitral stenosis. To be noted are (1

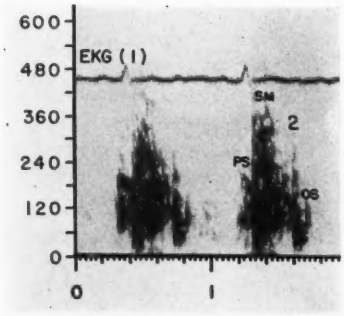

FIG. 10. Recorded at apex three years after valvulotomy for clinically "pure" mitral stenosis. See text.

the decrescendo type of systolic murmur of the mitral regurgitation created at operation, (2) the opening mitral "snap," and (3) the fact that the diastolic murmur is limited to presystole. The last phenomenon has been observed in other patients after operation.[13]

Some of the motion pictures which have been made of *in situ* functioning A-V valves demonstrate a low frequency flutter of the valve margin when the atrium contracts. The passive flow of blood into the ventricle in early diastole produces little vibration of the valve margins. The facts that the valve cusps have floated up toward the closed position when the atrium contracts and that increased velocity is imparted to the atrioventricular stream by atrial contraction may account for this marginal flutter in the normal situation. As for the postoperative state: these cases have no evidence of persistent obstruction of any significant degree. However, the anatomical state of the mitral leaflets is far from normal. They are irregular and present abnormal "tag ends" for vibration. They are stiffened to the point that they vibrate more noisily with atrial contraction. Atrial contraction may, in the postoperative period, still be unusually forceful as a result of the persisting hypertrophy of the left atrial wall. All of these considerations are consistent with the observation that the presystolic portion of the diastolic murmur is the first to appear and is the part present in cases of trivial mitral stenosis. In essence mitral valvulotomy tends to convert the patient from one with severe stenosis to one with mild stenosis and a varying amount (from none up) of mitral regurgitation.

The following features of interest are demonstrated by the patient (E. L., 227489) (with mitral stenosis and regurgitation and atrial fibrillation) from whose apical area the recording presented in figure 11 was made: (1) The low frequency content of the first apical sound is striking. This is a dull sound. (2) The systolic murmur is relatively high-pitched and is crescendo in frequency and intensity construction. This type of systolic murmur is to be compared with that in figure 10. (3) A third heart sound initiates the diastolic rumble. (4) There is no presystolic component to the diastolic murmur. (5) There may be a faint opening snap. (6) The rumble is decrescendo in intensity and to some extent in peak frequency. One would suspect predominant regurgitation in this instance and the suspicion is supported by ancillary clinical information on this patient.

The systolic murmur of mitral regurgitation is always holosystolic but it may be crescendo (see fig. 7b of Reference 3), decrescendo (see figure 10) or plateau in nature (see fig. 7 of Reference 4).

More often than not a third-sound gallop is

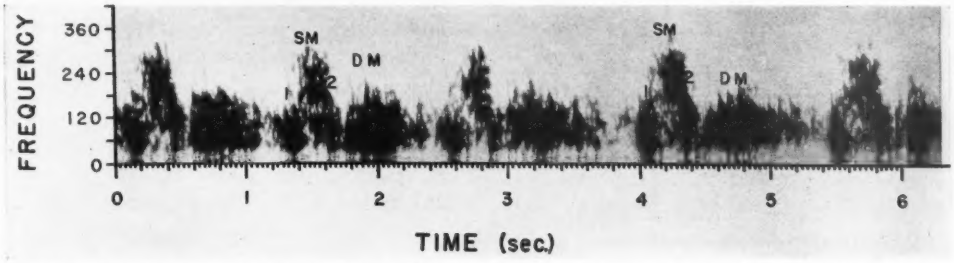

FIG. 11. Mitral stenosis and regurgitation with latter lesion predominating; atrial fibrillation. See text.

present with mitral regurgitation. This is probably due to increased volume and rate of diastolic filling of the ventricle. Not only the usual quota of blood enters the ventricle during each diastole but also that volume regurgitated during previous systole. This same factor, increased volume of mitral flow, is responsible for the diastolic rumble being louder than would be the case with the same degree of obstruction and no mitral regurgitation—mitral regurgitation tends to create a relative mitral stenosis. In this sense mitral regurgitation should be listed among the conditions which may simulate mitral stenosis.

Relative mitral stenosis can occur in two situations (usually both factors are operating in a given case): (1) Torrential flow through the mitral orifice and (2) dilatation of the ventricle without proportional dilatation of the mitral ring. The first factor is probably the leading one in the genesis of the middiastolic rumble which occurs with patent ductus arteriosus and interventricular septal defect, although dilatation of the ventricle is probably also present. The second factor is principally responsible in the genesis of the diastolic rumble which occurs early in acute rheumatic carditis. However, here too there is probably usually increased mitral flow since there is usually mitral regurgitation. In chronic anemia, such as that of sickle cell disease, the apical diastolic rumble is probably about equally the result of the ventricular dilatation and the increased flow accompanying anemia.

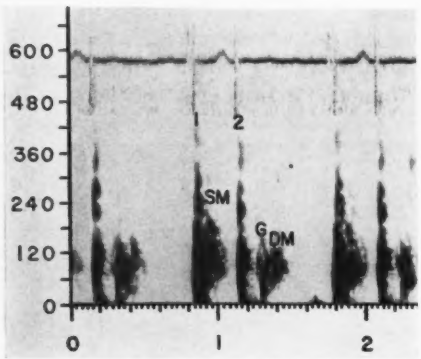

FIG. 12. Apical recording after exercise in patient with acute rheumatic fever.

In figure 12 is presented the recording at the apex after exercise in a patient (E. F., A58028) with active rheumatic carditis. Before exercise the systolic murmur and a much less conspicuous protodiastolic gallop were present. After exercise the gallop was exaggerated and was followed by a short rumble. During a course of cortisone in high dosage, the gallop and rumble became fixed even at rest. We have observed this same type of diastolic rumble initiated by a third sound gallop, in teen-age patients after cardiac decortication for constrictive pericarditis. In these there has been no reason to suspect organic mitral stenosis. The left ventricle has at times been evidently dilated.

Diseases of the Aortic Valve

The murmur of aortic stenosis has not only an intensity peak in midsystole as revealed by conventional phonocardiography (giving the familiar diamond configuration) but also a frequency peak in midsystole as revealed by spectral phonocardiography. This results in the characteristic Christmas tree shape shown in figure 13. The frequency peak occurs in this case at approximately the point midway between the first and second thirds of systole. It is clear from examination of this type of record why conventional phonocardiograms of the "high frequency" type usually demonstrate best the typical diamond configuration of ejection stenosis murmurs. (Fig. 15 presents the same "Christmas tree" pattern in the murmur of pure pulmonary stenosis of valvular type.)

Figure 13 presents the recording from the aortic area of a case of rheumatic heart disease with aortic stenosis and regurgitation. The gap between the end of the systolic murmur and the second sound and diastolic murmur is noteworthy. Poorly organized harmonics are also apparent in the systolic murmur. The simultaneous photographic and direct-written recordings presented in figure 2 for the sake of comparison were made from the aortic area of a patient with a "raspy" systolic murmur of calcific aortic stenosis. It is seen that the raspy quality is attributable to the presence of

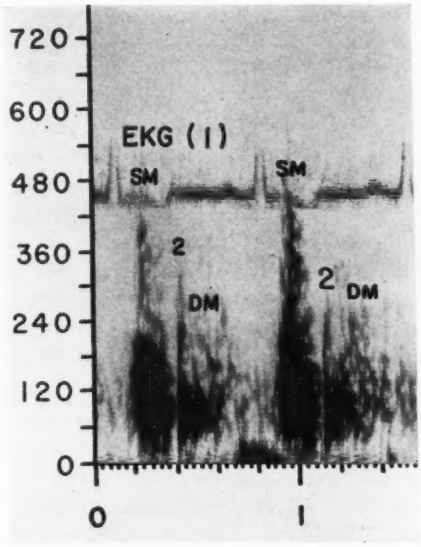

FIG. 13. Aortic area in aortic stenosis and regurgitation on rheumatic basis. Note Christmas tree configuration of systolic murmur, gap between murmur and second sound ("2"), diastolic murmur decrescendo in both intensity and peak frequency.

harmonics and the particular frequency distribution of the overtones.

In hypertension the second sound in the aortic area becomes accentuated not only in intensity but also in peak frequency as indicated in figure 19. A "ringing" quality to the ear, manifested by the presence of harmonics in the spectrogram, is also acquired. Similar alterations in the second aortic sound may occur in the absence of hypertension if structural changes occur in the valve cusps altering their vibrational characteristics. A ringing, accentuated second aortic sound is characteristic of sclerosis of the aortic cusps. It has in the past been accepted as *prima facie* evidence of syphilitic aortitis.[17] Since intimal changes of atherosclerotic nature occur at the level of the sinuses of Valsalva and on the aortic cusps themselves as a secondary effect of syphilitic aortitis, a ringing aortic second sound in syphilitic aortitis may have a basis in these changes. However, the sign would seem too nonspecific to be used as more than supporting evidence for the diagnosis.

Early in rheumatic aortic valvulitis, before

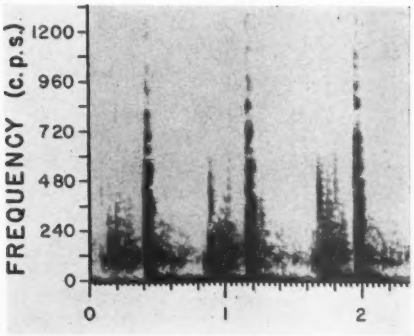

FIG. 14. Aortic area in 15 year old girl with early aortic valvulitis on a rheumatic basis. Second aortic sound (A2) is very ringing in character with harmonic pattern and accentuation of both intensity and peak frequency. These changes may be due to valvular fibrosis. There is an early diastolic murmur.

or as aortic regurgitation develops, the second aortic sound may be accentuated in normotensive patients. A case in point is illustrated in figure 14. This 15 year old girl (N. B., 657032) has mild aortic regurgitation and normal blood pressure but a much accentuated second sound in the aortic area. This finding may be due to changes in the vibrational properties of the valve as a result of rheumatic fibrosis. Another contributing factor in the accentuated aortic second sound of rheumatic aortic valvulitis when aortic regurgitation is present may be the "systolic collapse" phenomenon of Wiggers. Because of the lower diastolic pressure against which the ventricle is ejecting, ejection occurs earlier in systole with a higher systolic pressure peak and a sharp collapse of the pressure curve after this peak. This rapid fall in pressure may result in accelerated aortic valve closure and an accentuated second heart sound.

There are, then, two mechanisms for ringing second aortic sound: (1) Increased force of closure as in diastolic hypertension and (2) stiffening of the valve cusps. Both may be factors in a given case.

GALLOPS

Figure 15 presents an example of atrial gallop which occurred in a patient with pure pulmonary stenosis of valvular type (J. B., 680181). Note the characteristic appearance of

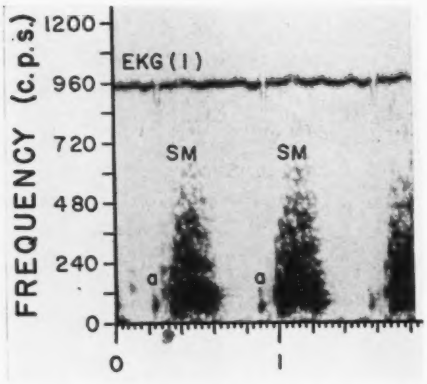

FIG. 15. Presystolic gallop ("a") in association with pure pulmonary stenosis. Note Christmas tree configuration of this ejection stenosis murmur.

this ejection stenosis murmur. Figure 16 presents the recordings in four areas of a patient (W. B., 593724) with severe arterial hypertension. Again there is a striking presystolic or atrial gallop loudest at the apex. In the aortic area there is a faint early systolic click of the type frequently seen in aortic atheromatosis, aortic dilatation, syphilitic aortitis or hypertension (see below). Of these two cases of presystolic gallop, the extra sound presumably arises in the right side of the heart in the case of the first and in the left side in the case of the second.

The patient (A. E., 299576) from whom the recording in figure 17 was made has very marked delay in atrioventricular conductions as indicated by the long P-R interval in the electrocardiogram. There is a striking atrial, or presystolic, gallop ("a") in this recording from apical area. The first sound is indistinct and merges indistinguishably with the systolic murmur. The second sound is likewise difficult to identify. The patient has aortic regurgitation and stenosis and mitral regurgitation. The early diastolic murmur may be transmitted from the aortic area. The fact that the atrial sound is followed by no murmur, comparable to the presystolic murmur of mitral stenosis with sinus rhythm and a normal P-R interval, suggests that mitral stenosis is not present. Nylin[19] demonstrated such a murmur after the auricular sound in a patient with heart block and mitral stenosis. In brief, this is a case of atrial, or presystolic, gallop in which the gallop sound was rendered mesodiastolic in timing by the prolongation of atrioventricular conduction.

Figure 18 presents another mesodiastolic gallop recorded at the tricuspid area in a patient (C. C., 196902) with severe hypertension. This is probably a summation gallop since in many cycles slight splitting of the gallop sound

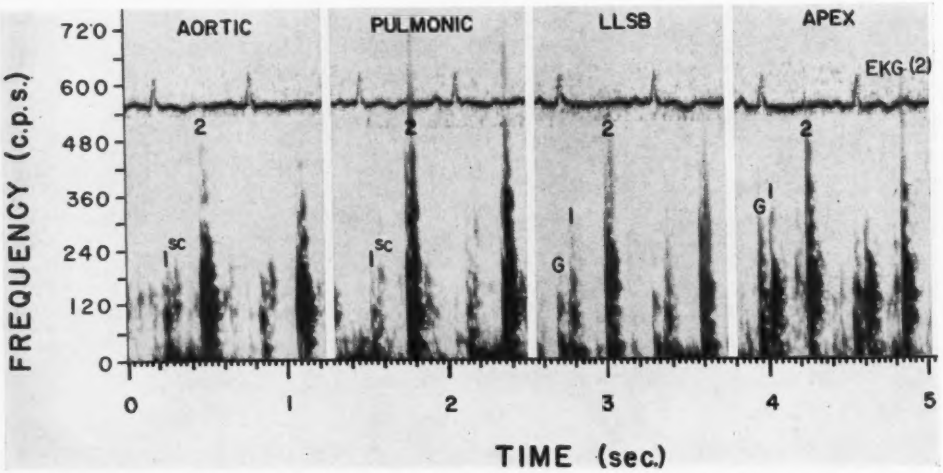

FIG. 16. Recorded at areas indicated in patient with malignant hypertension. Note early systolic click at base and the presystolic gallop.

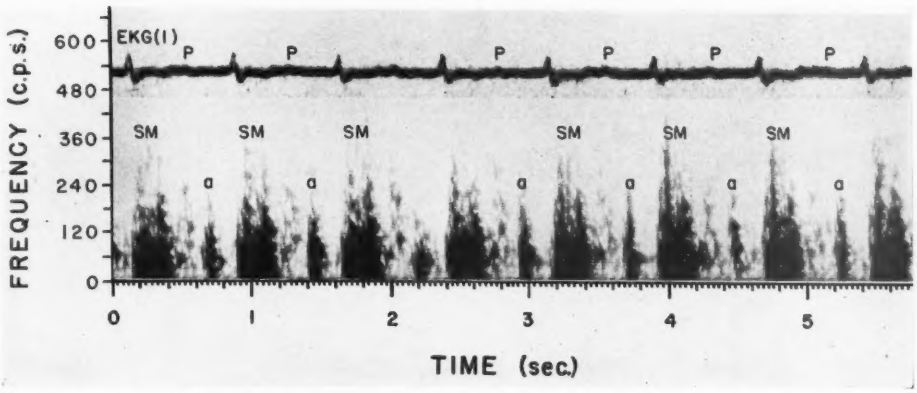

FIG. 17. Recorded at apex in patient with aortic stenosis and regurgitation on a rheumatic basis and with much delayed atrioventricular conduction. A presystolic gallop ("a") is "moved back" into mid-diastole. First apical sound is muffled. The early diastolic murmur is transmitted from the base.

is discernible, the first component probably being protodiastolic and the second presystolic.

The patient whose heart sounds at the apex are pictured in figure 12 above had active rheumatic carditis with mitral regurgitation. The protodiastolic gallop ("G") so frequently present and seemingly due to hyperdynamic ventricular filling is displayed. (See section on disease of the mitral valve.)

SYSTOLIC CLICKS AND OTHER CIRCUMSCRIBED SYSTOLIC SOUNDS

Systolic clicks and other circumscribed systolic sounds can be classified as to mechanism in the following manner:

I. Those due to arterial abnormalities.
   a. Dilatation of the pulmonary artery, as in mitral stenosis, interatrial septal defect, patent ductus arteriosus.
   b. Dilatation of the ascending aorta, as in atherosclerosis, hypertension and syphilitic aortitis.

II. Those arising by extracardiac mechanisms.
   a. Pleuropericardial adhesions.
   b. Placques of calcification in the pericardium.
   c. Grating of xiphosternal, costochondral or chondrosternal joints by ventricular contraction.
   d. Uncoiling and dilatation of auricular appendage with mitral regurgitation.

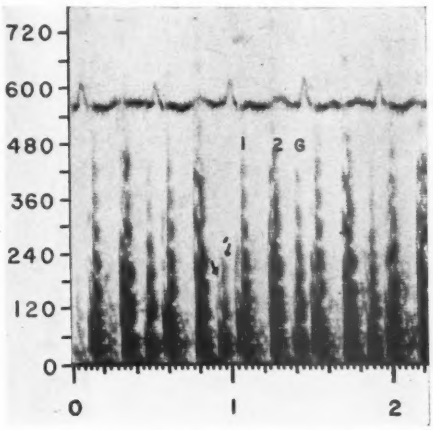

FIG. 18. Mesodiastolic gallop; probably a summation gallop.

   e. Systolic expansion of ventricular aneurysm.[20]
   f. Mediastinal emphysema.[21]
   g. Left pneumothorax.[22]

III. Atrial sound in midsystole due to low nodal ("infranodal") pacemaker with retrograde conduction.[23]

Figure 19 is the spectral phonocardiogram from the aortic area in a patient (E. W., 782911) with severe arterial hypertension. The accentuated second sound is very striking. Attention is called to the early systolic click. The patient, 33 years old, has mild dilatation

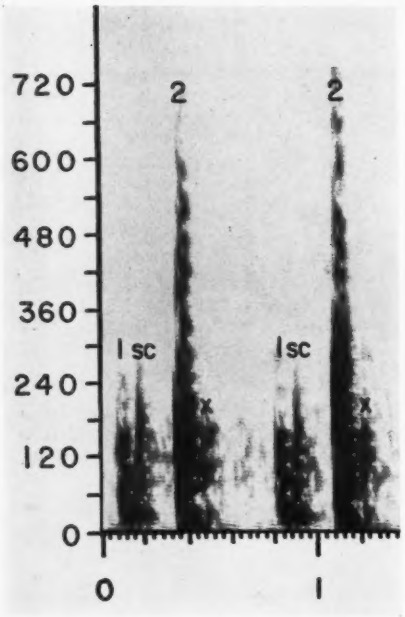

FIG. 19. Aortic area in arterial hypertension with dilated ascending aorta. Second aortic sound ("2") is accentuated in intensity and frequency. Note early systolic click.

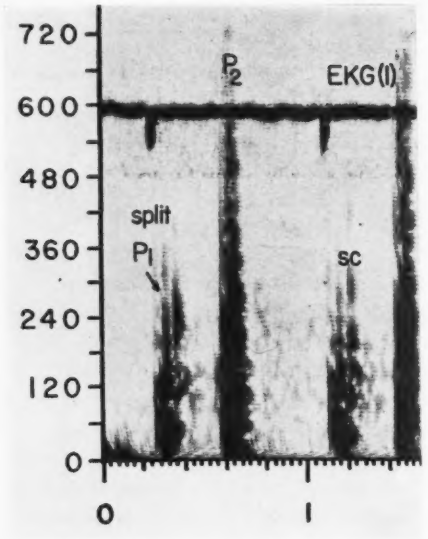

FIG. 20. Pulmonary area in patent interatrial septum with pulmonary hypertension. Second pulmonic (P2) is accentuated and first sound ("1") split. Note the early systolic click. The pulmonary artery was dilated.

and elongation of the aorta with "kinked" innominate-subclavian-carotid axis. The early click in hypertension was described by Potain.[24] A snapping of the aortic wall as it is distended by blood may be the mechanism. Leatham and Vogelpoel[25] observed an early systolic click in three cases of coarctation of the aorta, three of aortic stenosis, two of aortic insufficiency and two of aortic sclerosis. All of these had a dilated ascending aorta by x-ray study. In Leatham's experience the systolic click was usually about 0.07 second after the beginning of the first heart sound. A similar early systolic click in the aortic area in malignant hypertension is seen in figure 16.

Figure 20 presents the precisely comparable situation in the pulmonary area of a patient (Z. O., 673149) with interatrial septal defect, pulmonary hypertension and dilated pulmonary artery. The first sound, as well as the second, is slightly split, a common finding in atrial septal defect, even in the absence of bundle branch block. The early systolic click has an intensity concentration at about 240 cycles. In conventional phonocardiograms it is sometimes difficult to distinguish early systolic clicks from split first sounds. The spectral phonocardiograph has less difficulty in this regard. The sound looks like a "click," has "purer" frequency content than heart sounds usually do, and often does not have its frequency "bottom" at zero as do heart sounds proper.

Leatham and Vogelpoel[25] consider this variety of systolic click to represent "ejection vibrations" comparable to those recorded directly from the ascending aorta and pulmonary artery of dogs by Wiggers and Dean[26] in 1917. They are presumed to result from sudden tensing of the great vessel or abrupt attainment of its maximum capacity. Is it possible that the fundamental (seemingly at 240 cycles per second in the click of figure 20) represents the natural frequency of the pulmonary arterial wall in this patient? They are usually inaudible but may become audible when the pulmonary artery or ascending aorta is nearer the anterior chest wall, if the

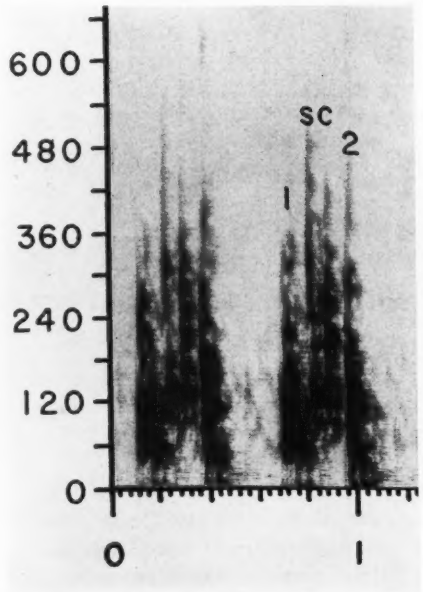

FIG. 21. Pulmonary area in patient with pronounced ascites.

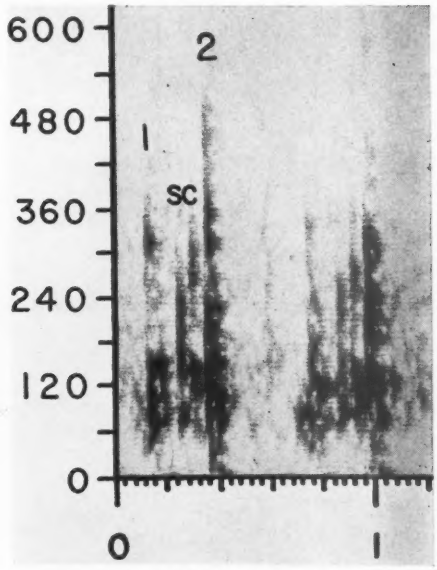

FIG. 22. Typical "xiphosternal crunch" (lower left sternal border). Note similarity to figure 2.

sound is delayed a bit, as in pulmonary or aortic stenosis, and if they are exaggerated by disease in the wall of the great vessel. The *sine qua non* appears to be dilatation of the great vessel. Leatham and Vogelpoel saw the early systolic sound in 44 cases of pulmonary hypertension with dilatation of the pulmonary artery and in five cases with only the dilated pulmonary artery. Lian and Walti[27] described it in pulmonary stenosis with dilated pulmonary artery.

In figure 21 is presented the heart sounds in the pulmonary area in a patient (M. B., 673169) with marked ascites. These adventitious systolic sounds changed virtually not at all with respiration and were fairly well localized to the area stated. We suspect they are produced by movement in costochondral and/or chondrosternal joints and that the pronounced abdominal distension is an important factor in their genesis, by displacement of the heart. The close similarity to the typical xiphosternal crunch (fig. 22) is to be noted. Note again the elevation of the frequency bottom in the case of these clicks.

In figure 22 is demonstrated a typical xiphosternal crunch.[28] As is frequently the case, confusion for pericardial friction rub occurred in this patient (O. F., 378868). The site of sound production in this situation appears to be the joints of the thoracic cage components in the region of the lower left sternal border. The occurrence of this sound predominantly or only when the subject is in the upright position is consonant with this view. It is doubtful in our minds that the xiphosternal joint often has anything to do with this sound; sternal, or chondrosternal, crunch might be a better name.

The late systolic click demonstrated in figure 23 was very loud over the entire precordium of M. G. (A15325), a 15 year old Negro girl who was observed in acute rheumatic fever a few months before this recording. During the peak of this disease, a pericardial friction rub was present. Subsequently the very loud systolic click developed. The chain of events provides circumstantial evidence for a pericardial origin of the click. Note the features that distinguish the click from a valve closure sound.

The striking systolic clicks displayed in figure 24 were recorded in a 58 year old woman

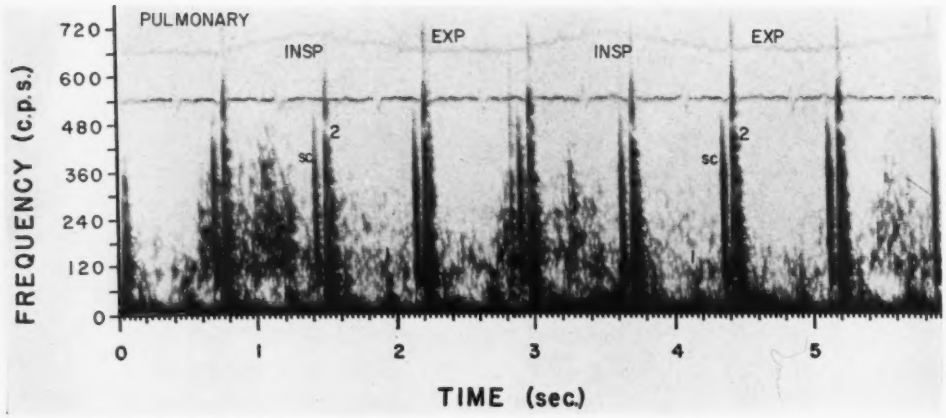

FIG. 23. Telesystolic click of probable pericardial origin.

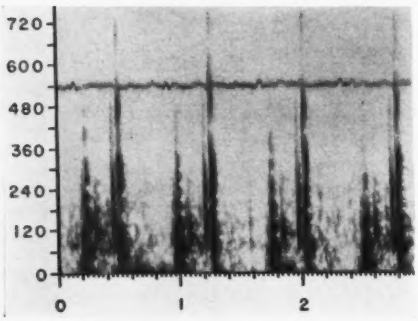

FIG. 24. Systolic clicks of doubtful origin. See text.

(688712) who had had acute rheumatic fever in youth (with, however, no evident valvular residua) and had mild *Trichterbrust*. The basis may be either pericardial adhesions, or movement of sternocostochondral joints, or both. The evidence that systolic clicks may result from pericardial adhesions was provided by autoptical correlations[29, 30] and by the observation fluoroscopically that localized tugging on the diaphragm occurred synchronously with the systolic click.[31] Note that the telesystolic click in the case illustrated in figure 24 does not have its frequency "bottom" at zero, a characteristic of systolic clicks.

Elsewhere[32] we have presented the spectral phonocardiograms of typical cases of systolic click producing so-called systolic gallop rhythm. Our studies would support the impressions of those[33] who doubt the existence of the entity called systolic gallop, at least this entity distinct from the systolic click. We have observed nothing except these short and high-pitched and therefore clicking sounds. Thompson and Levine[34] stated that 16 per cent of all gallops they encountered were systolic; from our experience this appears to be an accurate approximation of the incidence of systolic clicks. We are in agreement with the French school which refers to these sounds as "claquements" and decries the term "systolic gallop" customarily used in the English cardiological literature.

Figure 25a presents the recording of an early systolic click heard in a well-localized area at the apex. The heart sounds themselves are not remarkable. As is frequently the case with systolic clicks, the adventitious sound has its lowest frequency components at 60 cycles or higher rather than reaching the bottom level as in the case of the heart sounds proper. In this instance there are actually two systolic clicks, the first of which is exceedingly faint. Six years previously the patient (E. H., 452300) had staphylococcal endocarditis on the mitral valve, previously damaged, it was thought, by rheumatic fever. The patient probably has a moderate degree of mitral regurgitation and presents on fluoroscopy and roentgenkymography a most dramatic picture. With each systole the left auricular appendage uncoils, rises out of its bed in the A-V groove and probably expands as does the posterior

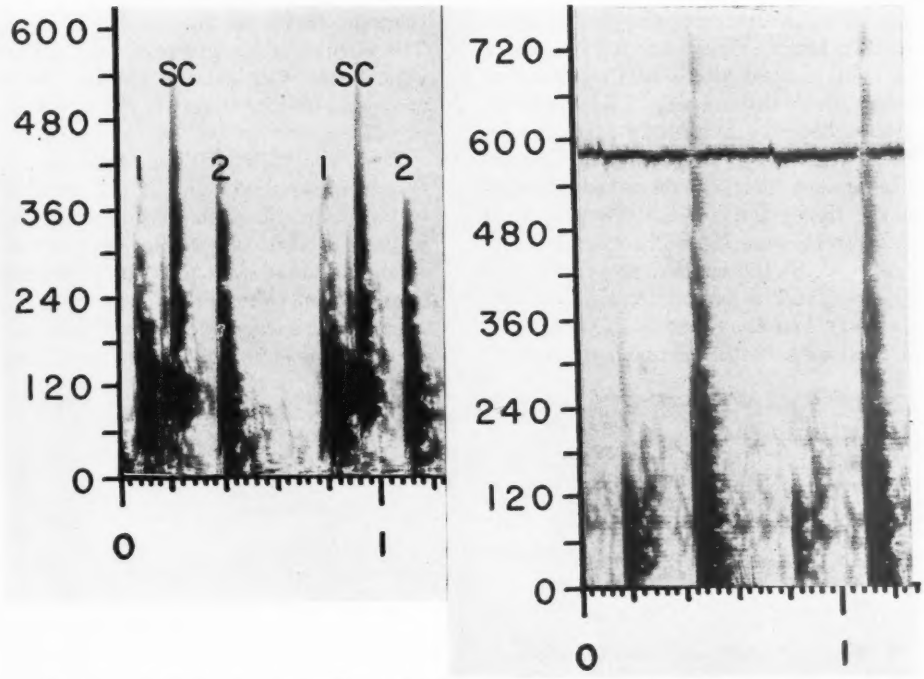

FIG. 25. a. Apex in case of uncoiling auricular appendage. See text. b. Left lower sternal border in case with anterolateral ventricular aneurysm. See text.

aspect of the left atrium. It may be this movement of the left auricular appendage which is responsible for this peculiar sound, perhaps through impact on the pericardium. The roentgenkymograms of this patient demonstrating this finger-like rhythmic outpouching of the left auricular appendage have been published elsewhere.[35] The mechanism of production of the systolic click in this case is comparable to that in ventricular aneurysm.[20] (Pericardial changes represent another mechanism for systolic clicks after myocardial infarction.)

The 50 year old patient (W. D., 684406) from whom the recording (at the lower left sternal border) in figure 25b was made has electrocardiographic evidence of an old anterolateral myocardial infarction and clear clinical and radiologic evidence of a ventricular aneurysm at the lower left heart border. The sound tracing reveals an early systolic click. This early systolic click is probably the result of expansion of the aneurysm in early systole. Pericardial adhesions are a less likely basis for the sound. In spite of the loud second sound the patient was normotensive. As was discussed above, this finding suggests sclerosis of the aortic cusps.

Closely related to systolic clicks both as to probable mode of genesis and as to prognostic significance are the circumscribed midsystolic

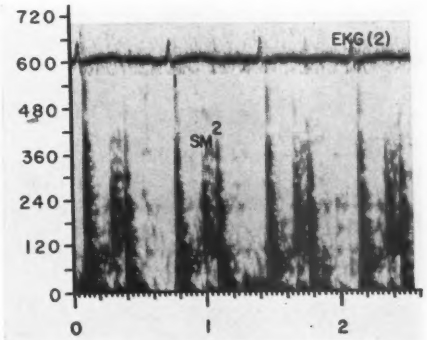

FIG. 26. Circumscribed late systolic murmur at apex in patient with history of rheumatic fever.

murmurs which are often introduced by a systolic click. There seems to be general agreement that these are extracardiac in origin, again being related probably to pericardial adhesions and/or roughening. Elsewhere[32] we have published an example of a systolic murmur which probably can be identified as innocent because it is circumscribed, is midsystolic in timing and is initiated by a systolic click. Figure 26 very forcefully illustrates the usefulness of the information proved by this type of display. The patient (A. H., A81746), 11 years old, had severe rheumatic fever two years previously. A persistent apical systolic murmur was occasion for concern, although no other signs of cardiac abnormality were present. The circumscribed character of the murmur with abrupt onset identifies the sound as extracardiac in origin. Obsolete pericarditis is the probable basis.

The identification of the type of systolic sounds under discussion in this section has usefulness in connection with another not infrequent problem in cardiological practice: the differentiation of chest pain due to pericarditis from that due to coronary artery disease. Even though a pericardial friction rub is not present the presence of systolic clicks or of circun-

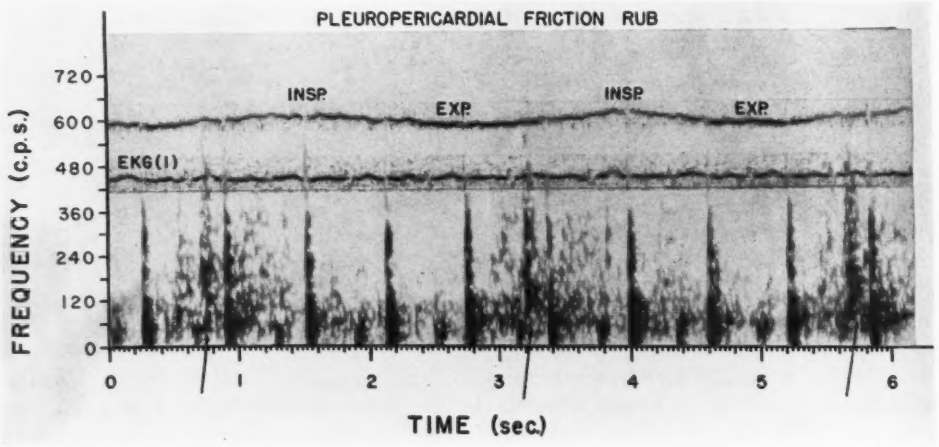

FIG. 27. In the midst of the normal inspiratory breath sounds there is a circumscribed sound which occurs at about the same point in inspiration (at the beginning) and in systole (early) on each occasion. Recorded in aortic area of patient with advanced pulmonary tuberculosis.

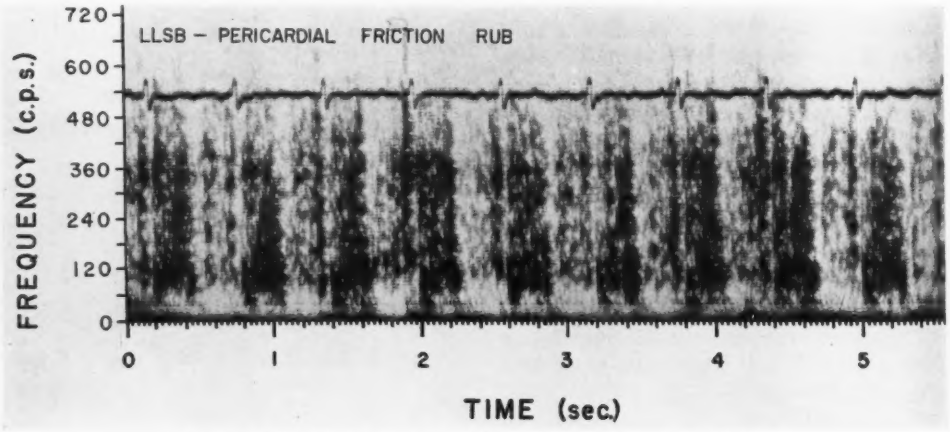

FIG. 28. Recording in patient with acute tuberculous pericarditis

scribed systolic sounds favors the diagnosis of previous pericarditis.

Other Sounds of Extracardiac Origin

In figure 27 is a recording from the aortic area in a patient with advanced pulmonary tuberculosis. With inspiration an early to mid-systolic scratchy sound developed. Three of these are marked with arrows. In the cardiac cycle immediately following the first two arrowed "scratches" a slight "scratch" is visible at the same point in systole. The sounds running through the heart sounds in the region of the scratches are typical inspiratory breath sounds. Note the clarity with which the "scratch" and the respiratory sounds can be distinguished. At times pleural and pericardial rubs may be difficult to distinguish clinically since the beating of the heart may generate sound in diseased pleura and pericardial frictions are prone to show pronounced variations with respiration. In this particular case there is no evidence of pericarditis: the scratch was confined to the second and third right intercostal spaces and there was no enlargement of the cardiovascular silhouette.

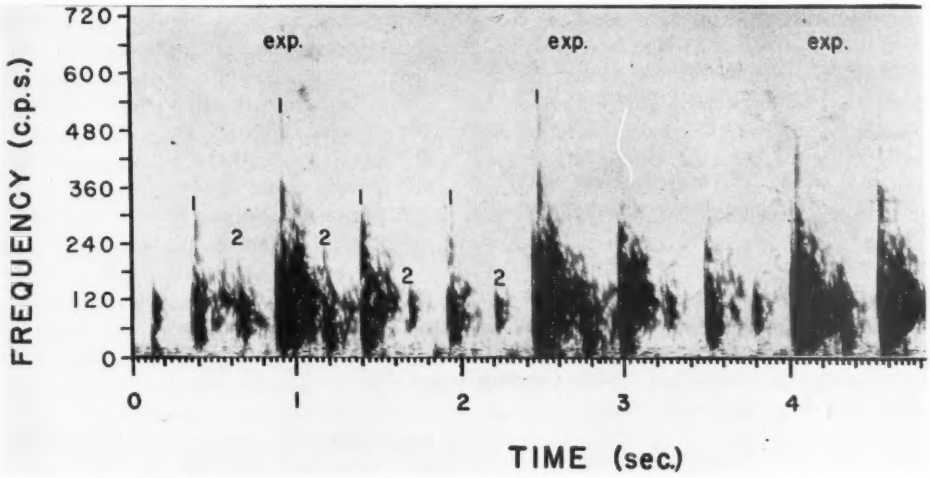

Fig. 29. Apex in patient with marked ascites. A *decrescendo* systolic murmur occurs in expiration.

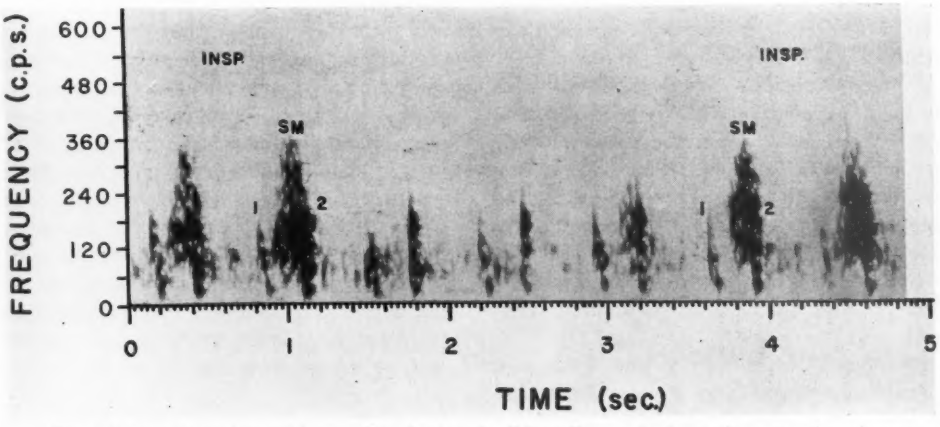

Fig. 30. Apex in patient with very flat chest and mild cardiomegaly due to hypertension. A *crescendo* murmur occurs in *inspiration*.

The recording in figure 28 was made from a patient with acute tuberculous pericarditis. There is a loud pericardial friction rub. It has an intensity-frequency-time pattern which is quite distinct from that of murmurs but which is more easily displayed than described. There are two areas of silence in the rub: (1) after atrial contraction but before ventricular contraction and (2) just after the second heart sound during isometric relaxation. There are three main periods to the rub: systolic, protodiastolic, and presystolic.

In figure 29 is shown the recording from the pulmonary area in a patient (W. B., 674663) with pronounced ascites due to Laennec's cirrhosis. There was tachypnea and tachycardia. With *expiration* an *early* decrescendo systolic murmur developed. Autopsy revealed no abnormality in the heart and surrounding tissues. In figure 30 is shown the apical recording in a patient (P. R., 364990) with a very flat chest and mild cardiomegaly due to renal hypertension. The contrast with the case in figure 29 is of great interest. In this case the extra sound is *late* systolic and *crescendo* and occurs in inspiration. These cardiorespiratory murmurs probably find ready explanation in pulmonary compression by the beating heart or possibly in the rubbing of normal serosal surfaces.[36]

Summary and Conclusions

The conclusions from these studies are of two types: (1) those concerning the usefulness, realized or potential, of spectral phonocardiography, and (2) those concerning cardiovascular sound as revealed by this method. Although few of these observations on cardiovascular sound are original to these studies, several are demonstrated in more convincing fashion than has previously been possible. The following observations on cardiovascular sound have been made: (Some of these have been discussed very little here but are covered in more detail in other publications from this laboratory.)

1. In general intensity and peak frequency (or frequency range) vary in a parallel fashion in given heart sounds or murmurs. The louder a sound or murmur, or a portion thereof, the higher is its frequency span. For example, the murmur of aortic stenosis, described as diamond-shaped because of its intensity peak in midsystole as displayed by classical phonocardiograms, also has a frequency peak in midsystole. Similarly murmurs which are described as crescendo or decrescendo both as to intensity and as to peak frequency. (It is of interest that DeCastro[37] came to the same conclusion on the basis of stethoscopic estimation of pitch.) Accentuated heart sounds, such as the first sound at the apex in mitral stenosis and the second sound at the base in hypertension of the greater or lesser circulation, are accentuated in both intensity and in peak frequency. Other cases in point are the accentuated first sounds after shorter diastolic periods in atrial fibrillation and the cyclical variations in the continuous murmur of patent ductus arteriosus, Blalock-Taussig anastomosis and thyroid bruit.

2. In general, the more abrupt the physiological process producing the sound, the higher the frequency representation in the sound. Cases in point include the normal second heart sound, systolic clicks, opening mitral snaps, fetal heart sounds, and the sounds in children, small animals, and tachycardia. Dull heart sounds, sounds of so-called "poor quality," usually lack components of higher frequency, due in part to slower, less "snappy" closure of the valves.

3. Since they are total and detailed representations of cardiovascular sound, spectral phonocardiograms display timbre (quality) and permit its description in physical terms. The following are specific points in this connection:

a. "Ringing," "tambour," "pistol-shot" have their physical basis in a short duration and in high frequency content (wide frequency span) with conspicuous harmonics.

b. Clicks and snaps are brief sounds with moderately high peak frequency and uniform intensity distribution over the frequency range, i.e., no harmonic banding. Frequently clicks and snaps do not have their frequency bottom at or near "zero" as do the valve sounds.

c. Musical murmurs owe their acoustical properties to the presence of more or less wel-

rganized harmonic systems. The configuration f these systems as to timing, intensity and requency determines whether "rasping," shrill," "honking," "piping," "croaking" best escribes the particular murmur. Slopes in, or urvature of, harmonics in musical murmurs an be related to hemodynamic variations at he generator.

d. The low frequency content is the main haracteristic responsible for the rumbling uality of the apical diastolic murmur in mitral tenosis.

4. At least partial explanation is provided or the frequent failure of conventional phonocardiography to demonstrate the typical diamond-shape of "ejection stenosis" murmurs, the crescendo character of the presystolic murmur of mitral stenosis or the decrescendo of aortic regurgitation: the contribution of the higher frequencies is not recorded because of lack of sensitivity in that range.

5. Since artefacts such as borborygmi, breath sounds, hiccoughs, electrical interference, speech sound can be identified in the spectral phonocardiogram, they are less likely to occasion confusion.

The usefulness of spectral phonocardiography in clinical and physiological investigation is indicated by the above. In general, the spectral phonocardiogram resembles closely the mental image of heart sounds and murmurs. As much information can be displayed in the spectral phonocardiogram as can be made out by the auditory mechanism; still more can be displayed since the spectral phonocardiogram suffers from no physiologic masking, no fatigue phenomena, and no peculiarities of intensity response at various frequency levels, and since it has a time resolution superior to that of the ear. The resolution of this method in the time dimension is put to test in the display of minute splitting of heart sounds. The improved resolution of time results from the spreading out of the frequency spectrum: even if splitting is not discernible at points of higher intensity, it is likely to be evident in other areas of lower intensity. The spreading out of the frequency spectrum permits a display of the full dynamic range of cardiovascular sound; for example, a very faint diastolic murmur can be accurately displayed in its true proportions in the presence of very loud systolic murmur.

Since it emulates the ear, spectral phonocardiography is ideal for teaching clinical stethoscopy, for detailed presentation of these sounds on the printed page and for precise, quantifiable recording of the course of certain forms of heart disease and the effects of some types of cardiovascular surgery.

Summario in Interlingua

Phonocardiographia spectral es un adaptation del methodo phonospectrographic disveloppate al Laboratorios Telephonic Bell. Illo differe ab phonocardiographia oscillographic conventional principalmente in le facto que illo monstra non solo le dimensiones de tempore e intensitate sed etiam spectros de frequentia. Iste ultime facto explica tres avantages del methodo: (1) Illo provide un definition physic del qualitate o timbro del sono. (2) Illo permitte un meliorate resolution del dimension temporal. (3) Le extendite scala dynamic del sonos cardiovascular es plus clarmente demonstrabile in illo.—Iste methodo es capace o pote esser disveloppate a devenir capace a facer toto lo que le aure es capace a facer. Illo probabilemente pote equalar le attingimentos del aure proque (1) illo non es restringite a un specific curva de responsas de frequentia e intensitate, (2) illo non suffre de ulle impedimento "psychoacustic," (3) illo provide un melior resolution del dimension temporal, e (4) illo produce permanente e quantificabile registrationes. In le presente reporto es discutite seligite aspectos de morbo del valvula mitral, de morbo del valvula aortic, de galopo, del clic systolic, e de sonos extracardiac. In general, intensitate e frequentia maximal varia parallelmente in sonos de origine cardiovascular. Artefactos debite a sonos del ambiente noncardiovascular e a interferentia electric es identificabile e pote esser disconsiderate in le analyse del sono cardiac.

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The Significance of the Serum Glutamic Oxalacetic Transaminase Activity Following Acute Myocardial Infarction

By JOHN S. LADUE, M.D., PH.D. AND FELIX WRÓBLEWSKI, M.D.

The serum glutamic oxalacetic transaminase rose two to 20 times normal in 74 of 75 patients who had acute transmural myocardial infarction. The height of the enzymatic activity was roughly proportional to the size of the infarct. Serum glutamic oxalacetic transaminase is unaffected by angina pectoris, coronary insufficiency, heart failure, or digitalis in the absence of active heart cell injury. Experimental myocardial infarction is followed consistently by a two to twenty-fold increase in serum glutamic oxalacetic transaminase activity. Increase in the serum activity of this enzyme appears to be a useful index of the presence of active heart muscle injury.

SERUM glutamic oxalacetic transaminase (SGO-T) is widely distributed in animal tissues but is most concentrated in heart muscle. This property led us to study its concentration in human serum following acute myocardial infarction. Serum glutamic oxalacetic transaminase permits the enzyme catalyzed reversible transfer of the alpha amino nitrogen of aspartic acid to alpha ketoglutaric acid with the synthesis of glutamic and oxalacetic acids as shown in figure 1. Table 1 indicates the relative rate of transamination by heart muscle, skeletal muscle, brain, liver, kidney, testis and lung.[2]

Earlier studies employing paper chromatography demonstrated that glutamic oxalacetic transaminase was present in normal human serum.[5] The enzymatic activity was shown to be stable in serum stored at 0 to 5 C. for periods of up to two weeks and neither freezing nor lyophilization appreciably altered the transaminase activity. The level of serum glutamic oxalacetic transaminase in normal individuals is essentially the same from day to day and remains unchanged in sera stored at 0 to 5 C. for at least two weeks. Heating of the sera to 100 C. will destroy the activity. Table 2 compares the activity of the serum glutamic oxalacetic transaminase determined by paper chromatography with that obtained by the spectrophotometric method. The values are strikingly similar. A unit of activity is defined as a decrease in optical density of 0.001 mu per milliliter of serum per minute under the conditions described.[5] Glutamic oxalacetic transaminase activity has been demonstrated in all suitably processed sera. The concentration is the same in serum and plasma but is 10 times greater in hemolyzed red blood cells.

Normally the serum glutamic oxalacetic transaminase varies from 10 to 40 units per milliliter when tested at room temperature. Levels above this were not seen in patients with infectious, neoplastic, metabolic, or degenerative diseases in which acute destruction of heart, skeletal muscle or liver tissue could be excluded. There is a strikingly progressive increase in serum glutamic oxalacetic transaminase activity after death which is proportional to the expired time.[3]

Lyophilized coded sera from dogs subjected to acute myocardial infarction in Los Angeles in the laboratory of, and by the technique developed by, Agress, Glassner, and Clark at the Veterans' Administration Center were tested blindly in New York in our laboratory for serum glutamic oxalacetic transaminase.[1] Figure 2 summarizes the values obtained in animals which at postmortem examination were estimated to have 50 per cent, 20 per cent, and 5 to 10 per cent of their hearts infarcted. Figure 3 presents the same data, plotting the

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Supported in part by a grant from the New York Heart Association.

SPECTROPHOTOMETRIC TRANSAMINASE ASSAY

ASPARTATE + α-KETOGLUTARATE $\xrightarrow[\text{TRANSAMINASE}]{}$ GLUTAMATE + OXALOACETATE

OXALOACETATE + DPNH$^+$ $\xrightarrow[\text{MALIC DEHYDROGENASE}]{}$ MALATE + DPN

MICROMOLAR OPTICAL DENSITY $\left(\text{LOG}\frac{I_0}{I}\right)$ OF DPNH$^+$ ×6.22 λ=3400 Å

FIG. 1. Summarizes the chemical reactions involved in doing the assay on serum for glutamic oxalacetic transaminase. Note the dependence on a double system of enzyme and substrate for the analysis.

TABLE 1.—*Rate of Transamination for Various Types of Rat Tissue in Microliters per Milligram of dry Weight per Hour and in Micromoles per Gram of Fresh Tissue per Hour*

DISTRIBUTION OF TRANSAMINASE ACTIVITY IN RAT TISSUES

TISSUE	RATE OF TRANSAMINATION MICROLITERS MGM. DRY WT. HR.	MICROMOLES GM. FRESH TISSUE HR.
HEART MUSCLE	425	334
SKELETAL MUSCLE	316	289
BRAIN	260	264
LIVER	245	250
KIDNEY	245	269
TESTIS	150	126
LUNG	51	---
	--FROM F. P. COHEN J.B.C. 140:711 (1940)	--FROM J. AWAPARA J.B.C. 194:497 (1952)

peak serum glutamic oxalacetic transaminase levels versus the size of the estimated infarct. The data show that the height of the enzyme in the serum following myocardial infarction, is, under the conditions of these experiments, proportional to the size of the infarction.[4] Similar results have been found in dogs whose coronary arteries were ligated at varying levels, the degree of infarction being proportional to the height of the serum glutamic oxalacetic transaminase activity.[7]

FINDINGS IN HUMAN SUBJECTS

The sera of 50 patients who had unequivocal transmural myocardial infarctions were analyzed for serum glutamic oxalacetic transaminase activity at varying times during the first three to 30 days following the onset of chest pain. The sera of 17 of these patients were coded and sent refrigerated from Syracuse

TABLE 2.—*Comparison of Serum Glutamic Oxalacetic transaminase Activity of Human Serum in Micromoles per ml. of Serum per Hour as Determined by Paper Chromatography and by Spectrophotometry*

SERUM TRANSAMINASE ACTIVITY UPPER LIMIT OF NORMAL

METHOD	UNITS Ml. SERUM MIN.	MICROMOLES Ml. SERUM HR
1. PAPER CHROMATOGRAPHY ASPARTATE - 50 MM. KETOGLUTARATE - 50 MM. AT 37° C.		1.00
2. SPECTROPHOTOMETRY ASPARTATE - 100 MM. KETOGLUTARATE - 20 MM. AT 25° C.	32	0.96

University through the courtesy of Dr. Richard Lyons and were analyzed in our laboratory. The serum glutamic oxalacetic transaminase activity was correlated with the clinical course much later. Characteristic serum glutamic oxalacetic transaminase curves with time were obtained in every instance save one. The fact

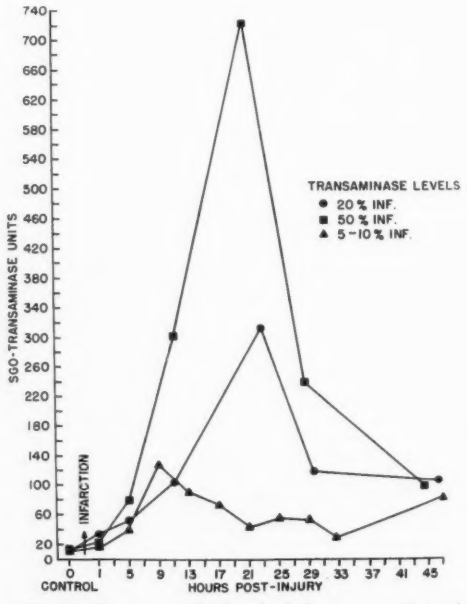

FIG. 2. Compares the level of the serum glutamic oxalacetic transaminase at varying periods following infarction of 50 per cent, 20 per cent and 10 per cent of dog hearts.

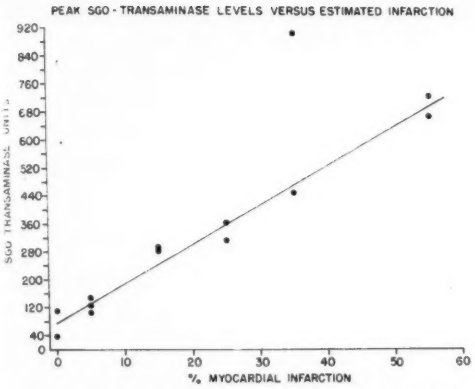

FIG. 3. Plots the highest levels of serum glutamic oxalacetic transaminase seen following experimental infarction of 5, 15, 25, 35 and 55 per cent of the dog heart.

that this serum was drawn on the third day after the onset of pain and was then stored for 21 days prior to analysis may in part explain the discrepancy. It is also possible that infarction occurred two or three days prior to the onset of chest pain.

Figure 4 describes the serum glutamic oxalacetic transaminase activity in a 60 year old white man who developed crushing substernal pain at time zero associated with shock, mild heart failure, and classical electrocardiographic evidence of a large posterior infarct. The serum glutamic oxalacetic transaminase was within normal limits three hours post injury but rose to 500 units within 12 hours, falling off gradually to normal by the sixth day. Figure 5 describes similar serum glutamic oxalacetic transaminase changes in a 36 year old white man with levels of 160 units six hours after the onset of his pain, rising to 430 within 24 hours and falling to 90 by the third day at which time the patient again complained of substernal pain associated with shock. The serum glutamic oxalacetic transaminase levels were 215 on the following day, falling to normal six days later. Note the lack of correlation with the sedimentation rate and white blood count. We have studied four additional patients who have developed secondary serum glutamic oxalacetic transaminase elevations sometimes associated with pain but always clinically compatible with extension of previous infarction.

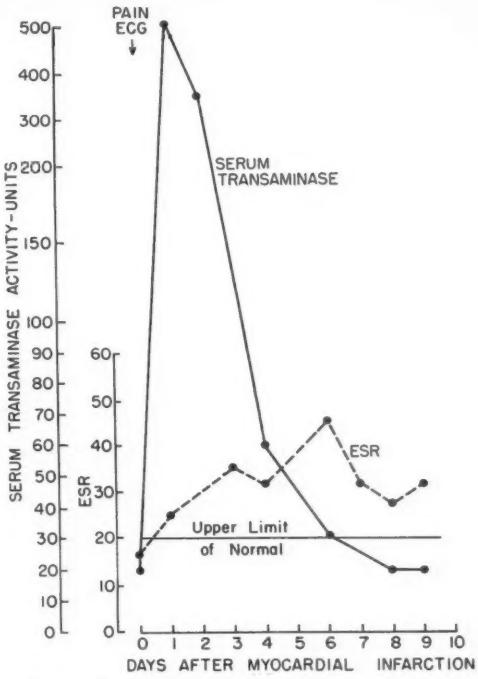

FIG. 4. Represents a typical example of serum glutamic oxalacetic transaminase elevation following acute human myocardial infarction. Note that the serum glutamic oxalacetic-transaminase was within normal limits three hours following the onset of pain but rose to 500 units within 12 hours.

Figure 6 summarizes the serum glutamic oxalacetic transaminase activity on various days post injury in 50 patients with transmural myocardial infarction. The horizontal line indicates the level for the number of patients from which the average was computed and the bottom and top of the vertical lines represent the low and high values in the sera tested on the indicated day. By the third day 10 patients had serum glutamic oxalacetic transaminase levels of 40 or less, by the fourth day 17 patients, by the fifth 21, by the sixth 26, and all the rest were below 40 units by the seventh day unless evidence of further infarction developed. Two patients with levels of 5000 and 6000 units on the second day, proven at autopsy to have large myocardial infarctions, were not used in computing the data for this chart, which is representative of the average observations. Both of these patients also had active liver

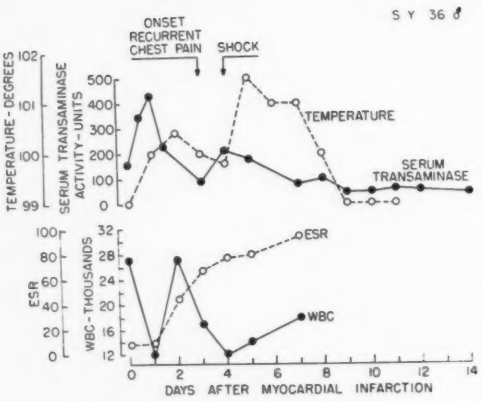

FIG. 5. Plots the serum glutamic oxalacetic transaminase levels following acute infarction complicated on the third day by recurrent chest pain associated with a second rise in serum glutamic oxalacetic transaminase believed to represent extension of the first infarct. Note the lack of correlation between the white blood cell count, erythrocyte sedimentation rate, and temperature and the level of the serum glutamic oxalacetic transaminase.

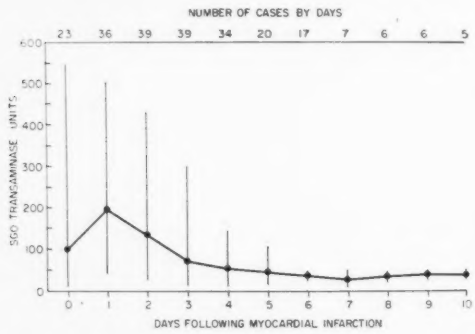

FIG. 6. Summarizes the serum glutamic oxalacetic transaminase activity on various days post injury in 50 patients with transmural myocardial infarction. The heavy horizontal line connects dots representing the average level of serum glutamic oxalacetic transaminase and the bottom and top of the vertical lines the low and high values tested on the indicated day. The numbers on the top of the figure indicate the number of patients from which the average, the high and the low values were obtained.

disease which we have found results in marked elevations of the serum glutamic oxalacetic transaminase. In one instance the serum glutamic oxalacetic transaminase was 1040 by the third day and in the other it remained elevated until death on the third day. Autopsy showed extensive antero lateral infarction and liver necrosis. Both patients were oliguric until death. These data suggest that serum glutamic oxalacetic transaminase is destroyed or changed in the liver, although renal block of excretion cannot be excluded.

The number of patients studied is relatively small, but we were unable to find any correlation between the height of the serum glutamic oxalacetic transaminase and the following clinical observations: age, sex, color, weight, height of temperature, level of the white blood count, the sedimentation rate, the presence or absence of shock, the absolute levels of the blood pressure, the presence of heart failure, the location of the infarction, the mortality rate, or the use of anticoagulant drugs. There was a significant correlation, however, between the serum glutamic oxalacetic transaminase level and the electrocardiographically estimated size of the infarct (the higher the enzymatic activity, the larger the infarct).

Serum glutamic oxalacetic transaminase levels have been determined in a wide spectrum of disease states and have not been found elevated in heart disease except that associated with active myocardial damage. In particular the values have been within normal limits in many patients with angina pectoris and coronary insufficiency even when the latter has been associated with the negative T-wave changes of ischemia. Serum glutamic oxalacetic transaminase has been normal following shock, heart failure, the use of cardiotonic drugs, cortisone, acute phlebitis, and cerebrovascular damage. It has been found elevated following acute myocardial damage, acute liver injury and following skeletal muscle damage after injury or surgery, after myositis including dermatomyositis, or arterial occlusion. The curve following acute myocardial infarction, however, has not been mimicked by any of the above disease states.

Serum glutamic oxalacetic transaminase rises precipitously following experimentally produced carbon tetrachloride liver damage. Liver cell injury in clinical carbon tetrachloride poisoning, in acute hepatitis, or in homologous serum hepatitis, is also associated with serum

glutamic oxalacetic levels of from 1000 to 12,000 units. Such marked elevations last for a few days but moderate enzymatic activity may persist for two or more weeks before falling to normal. In any event, the curve does not resemble that usually seen after acute infarction of heart muscle.*

Discussion

The level of serum glutamic oxalacetic transaminase following experimentally produced myocardial infarction almost invariably rises within four to six hours of the injury and remains elevated for from two to five days depending upon the extent of necrosis. The height of the serum glutamic oxalacetic transaminase is roughly proportional to the size of the infarct. This is true whether the infarction results from the injection of plastic spheres into the internal carotid, whether it is produced by ligation of coronary arteries in the closed chest or whether the muscle necrosis results from intravenous injection of papain.[1, 6, 8]

In addition to the 50 patients reported here in detail we have analyzed the serum of another 25 patients with transmural infarction and have found the serum glutamic oxalacetic transaminase elevations of from 70 to 600 units within 12 hours to 6 days post injury in every patient. In 30 instances the analyses were on coded sera thus excluding the chance of predetermination. The single patient who failed to show an increase of enzymatic activity after infarction has already been discussed. Figure 7 shows that the higher the enzymatic activity is, the longer such elevation persists. Since in dogs the height and duration of serum glutamic oxalacetic transaminase activity was proportional to the size of the infarct, we believe a similar finding in humans indicates at least a rough correlation between the amount of muscle necrosis in human myocardial infarction and the level of the serum glutamic oxalacetic transaminase.

Thirty-six patients with angina pectoris or coronary insufficiency, many showing ischemic

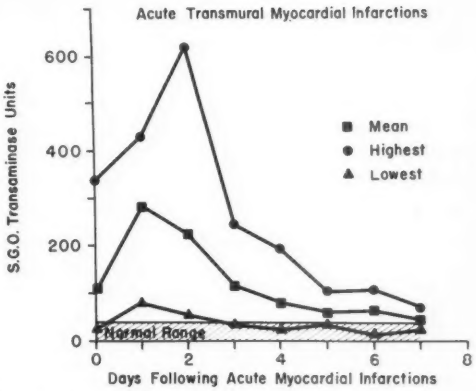

Fig. 7. Divides the serum glutamic oxalacetic transaminase curves following myocardial infarction in three groups: the connected squares represent the mean values, the circles the highest group of values and the triangles the lowest.

T-wave inversion or other equivocal electrocardiographic changes, have been studied and will be reported later in detail. Twenty-one had normal serum glutamic oxalacetic transaminase levels which fitted well with the classical picture. Fifteen with nonspecific electrocardiographic changes had elevated enzymatic activity of their serum, and therefore, presumptive evidence of heart muscle damage. Studies are in progress on serum glutamic oxalacetic transaminase in subendocardial infarction, following angina or coronary insufficiency associated with equivocal electrocardiographic changes, and in patients with acute rheumatic fever. When the enzymatic activity has been elevated in these patients, there has usually been some clinical evidence of active muscle damage.

Homogenized heart muscle of dogs contains approximately 400,000 units of serum glutamic oxalacetic per gram of homogenized tissue.[7] If all the enzyme present were released into the blood of a 30 Kg. dog the level in 1 ml. of serum would be approximately 400 units. That this is the mechanism by which serum glutamic oxalacetic is elevated following myocardial infarction is suggested by the fact that samples of infarcted heart muscle may contain as little as 4000 units per gram. Further evidence that the enzyme is released from damaged cells is

* Serum glutamic oxalacetic transaminase activity and liver injury will be the subject of another communication.

provided by the fact that serum glutamic oxalacetic transaminase rises precipitously and in proportion to the time elapsed after death of the mammal studied.[3]

Figure 8 shows the precipitous rise in serum glutamic oxalacetic transaminase following death. Of note is not only the magnitude of the elevation but the fact that samples from the jugular vein remain consistently low (40 units) when samples drawn from the superior vena cava at the same time may contain as much as 280,000 units. Since the enzyme is high in brain tissue there must be a blood brain barrier preventing the escape of serum glutamic oxalacetic transaminase from brain tissue into the circulation.

It is important to emphasize that infection, stress of various kinds, and metabolic, neoplastic, degenerative or congenital diseases do not alter the serum glutamic oxalacetic transaminase unless actual damage of tissue occurs. Thus, in neuromuscular, respiratory, cardiovascular, renal and skin diseases or blood dyscrasias in which active destruction of tissue can be excluded the serum glutamic oxalacetic transaminase is within normal limits. However, as in hepatitis, in some patients with rheumatic myocarditis, dermatomyositis and acute myocardial or renal infarction, the level of serum glutamic oxalacetic transaminase rises in proportion to, and as long as, acute tissue injury is going on.

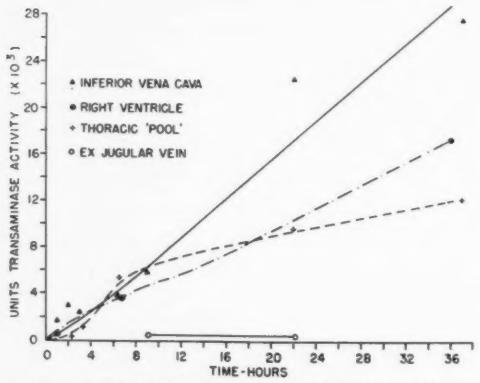

FIG. 8. Describes the serum glutamic oxalacetic transaminase activity of blood withdrawn four to 36 hours after death of a normal dog. Note the differences in enzymatic activity when blood was withdrawn from the inferior vena cava, the right ventricle, the thoracic pool and that secured from the external jugular vein.

The level of serum glutamic oxalacetic transaminase appears to rise concomitantly with acute damage of heart muscle or liver cells and would appear to be a useful tool in detecting not only the presence of active cellular injury of heart muscle but also, in a rough way, the degree of damage. Its usefulness in detecting muscle damage associated with angina pectoris, coronary insufficiency, rheumatic and other types of myocarditis holds promise but cannot be evaluated without further study.

The method of analysis is relatively simple, requiring only five minutes per determination. The results are reproducible in the same and different laboratories and the enzyme is stable for several days when stored at 0 to 5 C.

CONCLUSIONS

Serum glutamic oxalacetic transaminase was present in all human sera tested.

The normal range of activity at 20 C. is 8 to 40 units with a mean of 20 units.

Experimental myocardial infarction is followed consistently by a serum glutamic oxalacetic transaminase elevation of 2 to 20 times normal within 48 hours.

In 49 of 50 patients with transmural myocardial infarction serum glutamic oxalacetic transaminase activity rose 2 to 20 times normal during the first three days.

There appears to be a rough correlation between height of the serum glutamic oxalacetic transaminase activity and the size of the myocardial infarct.

Elevation of serum glutamic oxalacetic transaminase has been noted in conditions in which active destruction of heart muscle, skeletal muscle or liver occurs.

Serum glutamic oxalacetic transaminase is unaffected by angina pectoris, coronary insufficiency, heart failure, or digitalis in the absence of active heart cell damage.

Although serum glutamic oxalacetic transaminase appears to be an index of heart muscle destruction, its role in the diagnosis and management of heart disease will require further clinical study.

Conclusiones in Interlingua

Transaminase oxalacetic glutamic esseva presente in omne specimens de sero human examinate.

Le activitate normal a 20 C. varia inter 8 e 40 unitates con un valor median de 20 unitates.

Infarcimento myocardiac experimental es invariabilemente sequite intra 40 horas per un elevation del transaminase oxalacetic glutamic del sero a inter 2 e 20 vices le norma.

In 49 ex 50 patientes con infarcimento myocardiac transmural le activitate del transaminase oxalacetic glutamic del sero se augmentava durante le prime tres dies a inter 2 e 20 vices le norma.

Il pare exister un grossier correlation inter le magnitude del activitate de transaminase oxalacetic glutamic del sero e le dimension del infarcimento myocardiac.

Un elevation del activitate del transaminase oxalacetic glutamic del sero esseva observate in conditiones in que il occurre un destruction active del musculo cardiac, del musculos skeletal, e del hepate.

Le transaminase oxalacetic glutamic del sero non es afficite, in le absentia de active lesiones de cellulas cardiac, per angina de pectore, insufficientia coronari, dysfunctionamento cardiac, o digitalis.

Ben que le transaminase oxalacetic glutamic del sero pare esser un indice del destruction del musculo cardiac, su rolo in le diagnose e le tractamento de cardiopathia require studios clinic additional.

Acknowledgment

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Direct Arterial Study of the Blood Pressure Response to Cold of Normotensive Subjects and Patients with Essential Hypertension before and during Treatment with Various Antihypertensive Drugs

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The cold pressor test was performed three times at 15-minute intervals on 65 normotensive subjects and on 60 patients with essential hypertension both before and during treatment with antihypertensive drugs. The arterial pressure was recorded directly from the radial artery. On the basis of differences in the cold pressor response among individuals in the control group, the criteria for normal reaction and for hyperreaction were modified. The cold pressor response in the patients with essential hypertension was markedly depressed by the ganglionic blocking agents, but was not affected by various combinations of hydralazine, protoveratrine and reserpine.

IT HAS long been realized that variations in blood pressure occur throughout the day in both normal and hypertensive persons. The latter group, however, show more marked fluctuations of blood pressure than normal individuals in response to stimuli of equal intensity. Hines and Brown[1] demonstrated the phenomenon of vascular hyperreactivity by the cold pressor test. They arbitrarily considered a rise of blood pressure of more than 20 mm. Hg systolic and 15 mm. diastolic in response to cold to be abnormal, and placed their subjects into three groups according to the response of the blood pressure to cold. The first group consisted of individuals with usually normal blood pressures and a rise of less than 20/15 mm. Hg in response to cold. These subjects were called "normal reactors." The second group had normal blood pressures, but their blood pressures rose excessively during the cold pressor test and they were called "normal hyperreactors." The third group consisted of patients with essential hypertension.

In 1940, Hines[2] reported results of cold pressor tests on 1,015 persons with normal blood pressure and on 841 patients with essential hypertension. There were 859 normal reactors, and their mean rise of blood pressure in response to cold was 12.4/10.1 mm. Hg. One hundred fifty-six persons fell into the "normal hyperreactor group" with a mean increase of blood pressure of 31.2/27.5 mm. during the cold pressor test. The 841 patients with essential hypertension had a mean rise of blood pressure of 46.6/30.9 mm. in response to the cold pressor test. Hines postulated that the normal hyperreactors are in a "prehypertensive" phase of essential hypertension, and are likely to have the disease later. In a six-year follow-up of his original normal subjects, he found that none of the normal reactors had essential hypertension, whereas 38 per cent of the normal hyperreactors had developed this disease.

Since the first description of the cold pressor test, many investigators have reported their results, but relatively few have used Hines and Brown's exact technic. Hardgrove and associates,[3] Ayman and Goldshine,[4] Miller and Burger,[5] and Feldt and Wenstrand[6]

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Abridgment of thesis submitted by Dr. Windesheim to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

utilized Hines and Brown's technic and reported findings in close agreement with those of the latter authors.

The present study was undertaken in order to evaluate the response of blood pressure to cold as determined by an intra-arterial method of recording blood pressure, since this method allows a greater degree of accuracy than the indirect (cuff) method. Our major objectives were (1) to evaluate the consistency of the pressor response to cold when the stimulus was applied repeatedly, (2) to compare the cold pressor responses of control subjects with normal basal blood pressures with the response of patients with essential hypertension and (3) to determine the effect of antihypertensive drugs on the pressor response to cold in the patients with essential hypertension.

Methods

The control group consisted of 65 volunteers whose blood pressure was known to be normal. There were 30 men and 35 women. The mean age for the group was 26 years and ages ranged from 18 to 62 years. Results on 42 of the controls were taken from a previous study in the same laboratory by Dr. J. O. Godden.[7] The 60 patients with essential hypertension were chosen consecutively from those admitted to the hospital for treatment of hypertension. Individuals were excluded if they were found to have renal disease, Cushing's disease or other specific causes of hypertension, if they had been taking antihypertensive drugs or sedatives or if they were severely ill. All were ambulatory hospital patients. Their ages ranged from 35 to 71 years with a mean of 52 years. There were 38 men and 22 women.

The procedure was carried out in the following manner: The subject was allowed to rest in the supine position until the blood pressure became stabilized at its lowest or basal level. This period varied from 15 to 60 minutes. The blood pressure of most control subjects attained basal levels within 15 minutes, whereas at least 30 minutes were required for most of the patients with essential hypertension. The room temperature ranged from 73 to 76 F. and all extraneous noise was excluded.

A 20-gauge needle was inserted into the right radial artery through the skin which had been anesthetized with procaine hydrochloride. The indwelling needle was connected through polyethylene tubing to a three-way stopcock. This in turn was connected to a Statham strain-gauge manometer (15 P.S.I.) and the direct arterial pressure was recorded on a Sanborn multichannel recorder. Heparin was flushed through the stopcock periodically to insure patency. The site of puncture and the manometer were adjusted to the level of the midchest at the third intercostal space. The inner diameter of the arterial needle was 0.3 mm., and this was the smallest diameter of any part of the system. The dynamic response of the arterial pressure system, as measured on the pistophone,[8] showed that it was flat to 12 cycles per second, and the natural frequency of the system was 40 cycles per second. Respiratory excursion was recorded simultaneously on the Sanborn recorder by means of a face mask connected to another strain-gauge manometer and the electrocardiogram was also recorded simultaneously.

When the direct arterial pressure became stabilized at basal level, the first cold pressor test was performed. The exact technic of Hines and Brown was employed: The left hand was immersed in water at 4 to 6 C. to well above the level of the wrist for exactly one minute. This procedure was repeated twice more at intervals of 15 minutes. Thus three cold pressor tests were performed on all subjects whenever possible, but due to severe discomfort or technical difficulty we recorded only one or two in a few subjects.

The paper was run at a speed of 1 mm. per second between the cold pressor tests, but 30 seconds before immersing the hand in ice water, the speed was increased to either 5 or 25 mm. per second to allow a greater degree of accuracy in analysis. Thirty seconds after the cold pressor test was over, the speed was again returned to 1 mm. per second.

We analyzed the cold pressor response as follows: The 30 pulse waves immediately before the hand was immersed in ice water were used to determine the basal blood pressure before the cold pressor test. The maximal systolic and diastolic blood pressures were found by measuring the highest single pulse beat during or after the cold pressor test. This was done separately for the systolic and the diastolic pressure, since often the maximum for one did not occur in the same pulse wave as that for the other. Since there is some objection to comparing maximal pressure in a single beat with a mean basal pressure, we analyzed 10 records by measuring mean systolic and diastolic pressure in consecutive 10-second intervals for 90 seconds after immersion of the hand in ice water. It was noted that the maximal pressure occurred at the same time, and was only slightly less (1 to 3 mm. Hg systolic and diastolic) than by taking a single wave as the maximal blood pressure. For convenience, therefore, we continued using the latter measurement. Since it was almost impossible to determine accurately the time of return to basal blood pressure, the half maximal time was used as a measure of the rapidity of return to normal blood pressure. This was recorded by finding the first pulse wave after the maximal pressure that showed a blood pressure halfway between the basal and maximal pressures. This also was measured separately for

TABLE 1.—*Comparison of Cold Pressor Tests 1, 2 and 3*

Blood Pressure	Cold Pressor Test					
	No. 1		No. 2		No. 3	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
65 Control subjects						
Basal blood pressure, mm. Hg	115.80 ±1.93*	61.09 ±0.95	117.31 ±2.04	61.68 ±0.67	117.72 ±1.94	62.33 ±0.91
Response to cold						
Maximal pressure, mm. Hg	140.85 ±2.48	77.06 ±1.20	138.97 ±2.59	77.12 ±1.23	138.95 ±2.11	77.74 ±1.45
Rise, mm. Hg	25.05 ±1.53	15.97 ±0.97	21.36 ±1.29	15.44 ±0.82	21.23 ±1.50	15.41 ±1.05
Time to maximal pressure, sec.	54.54 ±1.83	54.24 ±1.62	54.57 ±1.45	54.69 ±1.56	54.91 ±1.87	55.48 ±2.06
Time to half maximal pressure, sec.	65.78 ±2.39	63.45 ±2.09	66.10 ±1.42	65.27 ±1.57	65.35 ±2.04	66.66 ±1.94
60 hypertensive patients before treatment						
Basal blood pressure, mm. Hg	201.98 ±2.44*	99.70 ±1.99	204.51 ±2.88	100.63 ±2.05	205.58 ±2.25	103.32 ±1.95
Response to cold						
Maximal pressure, mm. Hg	241.47 ±3.14	125.93 ±2.14	241.71 ±3.16	125.41 ±2.01	242.56 ±2.97	128.86 ±2.09
Rise, mm. Hg	39.49 ±2.17	26.23 ±1.78	37.20 ±2.19	24.78 ±1.39	36.98 ±2.27	25.54 ±1.43
Time to maximal pressure, sec.	55.83 ±1.09	53.65 ±1.33	53.56 ±1.51	53.07 ±1.60	56.97 ±1.46	55.81 ±1.26
Time to half maximal pressure, sec.	72.92 ±2.34	66.87 ±1.37	70.20 ±2.47	64.83 ±1.88	73.83 ±2.31	68.05 ±1.42

* Standard error of mean.

systolic and diastolic pressures, since they rarely occurred in the same pulse cycle.

The procedure was performed twice on the patients with essential hypertension in order to evaluate the effect of drugs on the cold pressor response. The first test was done the day after admission to the hospital, before treatment was started, and the second at the time of dismissal from the hospital.

RESULTS

Consistency of the Cold Pressor Response. The results of the three cold pressor tests, performed at intervals of 15 minutes, were compared. The results in the control group are shown in table 1. It is readily apparent that the basal and maximal diastolic pressures, as well as the increase in diastolic pressure in response to cold, were very constant, whereas the systolic pressures showed a slight, but statistically insignificant, variation. The time to reach maximal pressure and to return to half maximal pressure is also remarkably consistent.

The degree of hypertension was classed as 1 to 4 according to the Keith-Wagener classification of essential hypertension. Comparison of the results of the three cold pressor tests before and also during treatment of patients with hypertension of each group revealed no statistically significant differences. We, therefore, could compare cold pressor tests 1, 2 and 3 for the total hypertensive group of 60 patients before and during treatment (table 1). The result of comparison was very similar to that of the control group: The diastolic pressures were more constant than the systolic pressures but there were no statistically significant changes from test to test. The results of the three cold pressor tests, therefore, could be averaged and in the discussion from this point on we will consider only the mean of the three

TABLE 2.—*Response of Blood Pressure to Cold in 65 Control Subjects*

Control Group	Subjects	Cold Pressor Tests	Blood Pressure, mm. Hg					
			Basal		Response to Cold			
					Maximal		Rise	
			Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Total	65	182	116.90 ±1.14*	61.68 ±0.58	139.63 ±1.39	77.30 ±0.75	22.73 ±0.85	15.62 ±0.55
Normal reactors	36	102	112.05 ±1.00	59.76 ±0.62	129.21 ±1.11	70.88 ±0.60	17.16 ±0.56	11.12 ±0.45
Normal reactors	10	26	114.77 ±1.52	57.27 ±0.87	141.77 ±1.76	77.42 ±0.80	27.00 ±1.32	20.15 ±0.86
Normal hyperreactors	19	54	127.09 ±2.81	67.59 ±0.94	158.48 ±3.13	89.30 ±0.82	31.39 ±1.99	21.71 ±1.12

* Standard error of mean.

cold pressor tests of the control and hypertensive groups.

Responses of the Control Group to Cold Pressor Test. The findings in the control group of 65 subjects on whom a total of 182 cold pressor tests were performed are shown in table 2 and the figure. The average blood pressure response to cold for the group was a rise of 22.7/15.6 mm. but there were marked individual differences in response. We arbitrarily decided to consider the cold pressor response abnormal if the maximal diastolic pressure rose to 85 mm. or more by direct arterial measurement. By this criterion alone, there were 36 individuals whose maximal diastolic pressure did not reach 85 mm. Their mean cold pressor response was 17.2/11.1 mm., and they were considered to be definite "normal reactors." Nineteen subjects had a maximal diastolic pressure of 85 mm. or more in the cold pressor test and they will be referred to as "normal hyperreactors." Their average basal pressure was significantly higher than that of the normal reactors, and the average response of the blood pressure to cold was 31.4/21.7 mm. Hg. In a third group of 10 subjects, the maximal direct diastolic pressure did not reach 85 mm. Hg but response to the cold stimulus was in the same order as that of the normal hyperreactors (27.0/20.2 mm.). Their basal blood pressure was comparable to that of the normal reactors, and their maximal diastolic pressure was only 77.4 mm.

Responses of Hypertensive Group to Cold Pressor Test. The 60 patients with essential hypertension before beginning treatment had a mean basal blood pressure of 204.0/100.9 mm. Hg with a cold pressor rise of 37.9/25.8 mm. (table 3 and figure). A division into hypertension groups 1 to 4 made on the basis of funduscopic changes, revealed that the basal and maximal blood pressures gradually rose from group 1 to 4. The pressor response to cold was most marked in patients with group 2 hypertension (45.7/28.1 mm.) and next greatest among those with group 3 hyperten-

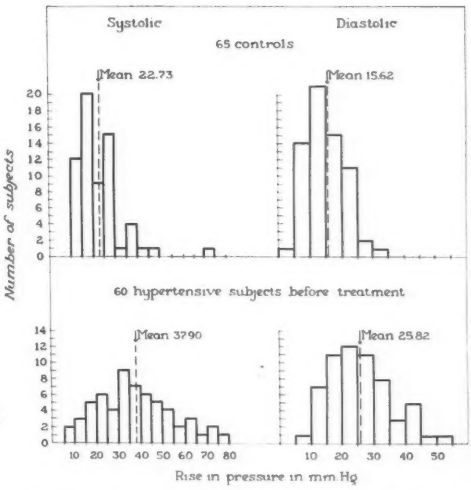

FIG. 1. The maximal response of the systolic and diastolic blood pressures of 65 control subjects and 60 patients with essential hypertension before treatment to the cold stimulus.

TABLE 3.—*Response of Blood Pressure to Cold in 60 Hypertensive Patients Before Treatment*

Hypertension	Patients	Tests	Blood Pressure, mm. Hg				Seconds from Cold Stimulus to			
			Basal		Response to Cold		Maximal Blood Pressure		Half Maximal Blood Pressure	
					Rise					
			Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Total	60	178	204.01 ±1.69*	100.87 ±1.16	37.90 ±1.27	25.82 ±0.88	55.46 ±0.79	54.17 ±0.81	72.32 ±1.14	66.58 ±0.90
Group 1	6	18	187.17 ±5.53	93.78 ±2.03	30.05 ±2.84	21.72 ±1.78	52.67 ±2.65	50.11 ±2.57	68.17 ±2.04	61.17 ±1.89
Group 2	24	72	195.85 ±1.99	95.24 ±1.74	45.65 ±2.00	28.11 ±1.42	56.51 ±1.03	55.75 ±0.99	75.14 ±1.90	68.18 ±1.34
Group 3	16	48	210.19 ±3.24	103.56 ±2.15	37.29 ±1.89	25.19 ±1.25	55.29 ±1.91	54.67 ±1.83	74.29 ±3.38	68.56 ±1.92
Group 4	14	40	218.88 ±3.32	110.98 ±2.15	28.20 ±2.64	21.97 ±2.29	55.00 ±1.52	52.58 ±1.89	66.75 ±2.80	63.78 ±1.97

* Standard error of mean.

sion. Patients with groups 1 and 4 hypertension demonstrated responses which were almost equal. Six of the 21 patients with essential hypertension, whose diastolic pressures rose 20 mm. or less in response to cold, had group 1 or 2 hypertension, five had group 3 and 10 group 4 hypertension.

During treatment, the same 60 patients had an average increase of blood pressure in response to cold of 34.0/20.0 mm. Hg. The average basal blood pressure which had been markedly decreased was 173.6/78.8 mm. and the average maximal pressure was 207.6/98.8 mm. Hg. This group will be discussed further later in this paper.

The time from immersion of the hand to maximal blood pressure was approximately equal in the control group and among the hypertensive patients before and during treatment, whereas the time of return to half the maximal blood pressure shows some variation. The tables demonstrate that the half maximal time is directly dependent on the blood pressure increase in response to cold. In general, subjects with the greatest blood pressure rise also had the longest half maximal times, and vice versa.

Effect of Antihypertensive Drugs on the Blood Pressure Response to Cold. The patients received various combinations of agents, and at the time of repetition of the procedure had been under treatment with the drugs at least one week, and most had been receiving treatment two to three weeks or more. Therapeutic results were considered adequate to allow the patients' dismissal from the hospital. The effect of the various drugs and combinations of drugs on the basal blood pressure and the maximal response to cold are given in table 4. The table has been arranged according to the height of the pretreatment basal diastolic blood pressure.

Eleven patients received a combination of protoveratrine and reserpine (Serpasil), which decreased the basal pressures from an average of 186.2/91.8 to 163.7/75.3 mm. without any effect on the cold pressor response. A similar result was observed in five patients receiving a combination of hydralazine and reserpine.

Thirteen patients received hydralazine hydrochloride (Apresoline), protoveratrine and reserpine. Their blood pressure was affected favorably by this combination, with an average decrease of 25.7/20.7 mm. during treatment, but there was little change in the cold pressor response during treatment. The response of the systolic blood pressure to cold was actually greater during treatment than before, but that of the diastolic pressure was slightly less.

Eleven patients, with an average basal blood pressure of 208.5/103.2 mm. before treatment, were treated with hexamethonium and reserpine. The mean basal blood pressure was decreased 27.4/19.6 mm. by these drugs

TABLE 4.—*Response of Blood Pressure to Cold Before and During Treatment With Antihypertensive Drugs*

Medication	Patients	Tests	Treatment	Blood Pressure, mm. Hg					
				Basal		Response to Cold			
						Maximal		Rise	
				Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Protoveratrine and reserpine	11	33	Before	186.21 ±2.86*	91.79 ±2.43	232.21 ±4.16	119.85 ±2.61	47.00 ±3.03	28.06 ±1.78
			During	163.70 ±3.09	75.33 ±1.56	212.52 ±2.28	102.58 ±2.83	48.80 ±1.93	27.25 ±1.58
Hydralazine hydrochloride and reserpine	5	15	Before	189.87 ±2.82	91.80 ±1.77	219.47 ±4.13	109.40 ±2.11	29.60 ±3.12	17.60 ±1.79
			During	164.60 ±4.82	73.00 ±2.13	193.80 ±5.17	90.40 ±2.94	29.20 ±2.87	17.40 ±2.01
Hydralazine hydrochloride, protoveratrine and reserpine	13	39	Before	206.95 ±4.60	98.44 ±1.41	249.79 ±3.33	128.85 ±2.57	42.84 ±2.82	30.41 ±2.05
			During	181.22 ±3.82	77.73 ±3.01	229.14 ±4.95	103.30 ±3.50	47.92 ±3.39	25.57 ±1.63
Hexamethonium and reserpine	11	32	Before	208.50 ±5.27	103.16 ±3.08	244.72 ±4.05	128.94 ±3.99	36.22 ±2.72	25.78 ±1.77
			During	181.06 ±3.78	83.52 ±1.72	210.76 ±4.11	103.06 ±2.82	29.70 ±2.21	19.54 ±1.50
Pentapyrrolidinium (M. & B. 2050)	4	12	Before	215.25 ±5.55	111.50 ±1.98	249.67 ±7.16	134.33 ±3.03	34.42 ±2.35	22.83 ±1.96
			During	189.00 ±5.54	91.83 ±3.44	205.75 ±4.59	103.75 ±3.76	16.75 ±1.76	11.92 ±0.94
Hexamethonium, hydralazine hydrochloride and reserpine	4	12	Before	208.58 ±5.27	115.75 ±4.01	242.08 ±4.16	135.75 ±3.87	33.50 ±2.61	20.00 ±1.73
			During	150.58 ±6.94	77.50 ±6.54	168.17 ±8.95	89.83 ±7.68	17.59 ±3.01	12.33 ±1.69
Hexamethonium and hydrazaline hydrochloride	6	17	Before	222.06 ±3.90	117.29 ±3.18	246.88 ±5.27	137.35 ±3.00	24.82 ±3.22	20.06 ±2.19
			During	170.56 ±5.27	82.00 ±1.79	184.83 ±5.66	90.39 ±2.38	14.27 ±2.49	8.39 ±1.05

* Standard error of mean.

and the response to cold was somewhat decreased from 36.2/25.8 mm. before treatment to 29.7/19.5 mm. during treatment.

Only four patients were treated with pentapyrrolidinium (M. & B. 2050) since only a limited amount was available at the time this study was conducted. This drug produced an average decrease of 26.3/19.7 mm. in the basal blood pressure. Before treatment, the rise in blood pressure in response to cold was 34.4/22.8 mm. whereas during treatment it was only 16.8/11.9 mm.

Hexamethonium, hydralazine hydrochloride and reserpine were given to four patients and also proved to be effective in decreasing the response of the blood pressure to cold, as well as causing a marked decrease, 58.0/38.3 mm. Hg in basal pressure.

The final group of six patients shown in table 4 was treated with the combination of hexamethonium and hydralazine hydrochloride. Again the basal blood pressure was markedly reduced by treatment from an average pretreatment level of 222.1/117.3 to 170.6/82.0 mm. on dismissal. During treatment the pressor response to cold was only 14.3/8.4 mm. whereas before treatment was begun it had been 24.8/20.1 mm.

Pulse Rates of Normal and Hypertensive Groups During Cold Pressor Test. The pulse rates in the control and hypertensive groups are shown in table 5. The rates were taken from the records made at the time of measurement of the direct arterial blood pressure. The "random" pulse was checked five minutes before immersion of the hand in water. The

TABLE 5.—*Change in Pulse Rate During the Cold Pressor Test*

Group	Subjects	Tests	Pulse Rate		
			Random (approx. 5 min. before Cold Pressor Test)	Prior to Immersion of Hand in Water	At Time of Maximal Diastolic Blood Pressure
Control	26	78	67.84 ± 0.98	68.84 ± 1.02	70.12 ± 1.03
Hypertensive (before treatment)	65	194	76.62 ± 1.06	78.08 ± 0.99	84.68 ± 0.99
Hypertensive (during treatment)	57	171	71.16 ± 1.00	72.23 ± 0.97	78.59 ± 0.93

pulse rate immediately prior to immersion and the pulse at the time of maximal diastolic pressure are also recorded in table 5. In all three groups, a slight, but statistically insignificant, increase in pulse rate occurred between the taking of the random pulse and the pulse prior to the cold pressor test. The pulse rates of the control group did not change appreciably during the cold pressor test while those of the hypertensive patients rose approximately 6 beats per minute during this period. This was noted both before and during treatment. Treatment caused a decrease of the pulse rate of 5 to 6 beats per minute.

DISCUSSION

The Method. The intra-arterial method of recording blood pressure allowed us to evaluate the rise in arterial pressure in response to the cold stimulus with greater accuracy. Whereas the indirect (cuff) method measures the blood pressure during one heart beat only, the continuous direct registration of arterial blood pressure allowed us to measure the response at any point on the record, during immersion of the hand in water and until the blood pressure returned to basal levels. The procedure is relatively simple, and we encountered no complications.

The Cold Pressor Test. The patients were all questioned as to the amount of pain noted during each of the three cold pressor tests. Nearly all experienced less discomfort during the second and third than during the first, yet the pressor response did not change from test to test. Although pain is a factor in the cold pressor response, there was no correlation between the severity of the pain and the blood pressure response to cold in this study.

The set of three cold pressor tests was repeated at intervals varying from 1 to 5 months on eight persons in the control group. Each one had almost exactly the same cold pressor response during both sets of tests. Although this group is small, it certainly seems that the response of the blood pressure to cold, especially that of the diastolic pressure, as measured by the direct method is constant for each person, whether the time between tests is 15 minutes or several months, provided the test is carried out by exactly the same method and in the same environment.

Significance of Excessive Reactions in Control Group. The application of cold caused some rise in blood pressure in all of the control subjects, but the amount varied markedly. The final significance of excessive reactions in the control subjects will be known only after follow-up for a number of years in order to note the development of essential hypertension, but certain suppositions are presented herein. We would expect essential hypertension to develop in few, if any, of the 36 (55.4 per cent) control subjects who were normal reactors, having a maximal diastolic pressure of less than 85 mm.

The incidence of essential hypertension among the 19 hyperreactors should be high in the future. The basal blood pressure for this subgroup was significantly higher than that of the other two control subgroups. Although there is no clear explanation for this phenomenon, it is possible that due to the marked vascular reactivity, basal levels were not attained in this group before the cold pressor test was begun. However, this is unlikely, since special attention was paid to the basal blood pressure, and the study was not done

until at least two to three cuff readings were at the same level after at least 15 minutes of rest. A second explanation is that mild subclinical essential hypertension may already be developing in some of the normal hyperreactors, thereby raising the basal blood pressure of the group. There must be a period at the onset of essential hypertension during which vasoconstriction is so mild that the measurements of blood pressure by the indirect method do not attain the diastolic level of 90 mm., which is the arbitrary upper limit of normal, although the disease is already present. Although none of the control subjects had a basal diastolic pressure by cuff reading greater than 87 mm. Hg, a significant number approximated this figure and all were hyperreactors.

The third control group, consisting of the 10 control subjects who showed a marked rise in blood pressure in response to the cold stimulus, but did not attain a maximal diastolic blood pressure (ceiling) of 85 mm. Hg by the direct method, will probably not have essential hypertension in the future. Although their blood pressures reacted more markedly to cold than those of the normal reactors, their mean maximal diastolic pressure was well within normal limits.

Since the cold pressor test is designed to measure peripheral vasoconstriction, the change in diastolic pressure should be the measuring stick of abnormality, for it is the indicator of peripheral resistance. Because of this, as well as the fact that the response of the systolic blood pressure to cold varies much more than the diastolic response, we have placed much more emphasis on the increase in diastolic pressure and the maximal diastolic pressure. In our opinion the criteria for abnormality of the cold pressor response should be not only an increase of 15 mm. Hg or more in diastolic blood pressure, but also a maximal diastolic blood pressure of 85 mm. or more by the direct arterial method (90 mm. or more by the indirect method). If both the rise in blood pressure and "ceiling" blood pressure are taken into account, fewer persons will be found to be vascular hyperreactors to cold, but they can definitely be considered to have abnormal vascular lability (the so-called prehypertensive phase of essential hypertension). If we now combine the two groups of "normal reactors," that is, those persons who either did not have an increase in diastolic blood pressure of 15 mm. or more in response to cold and those who had an increase in diastolic blood pressure of more than 15 mm., but did not have a maximal diastolic blood pressure of 85 mm. Hg by direct arterial measurement, we find that 46 (70.8 per cent) of the 65 control subjects were in the normal reactor group and 19 (29.2 per cent) can be considered to be normal hyperreactors.

Unfortunately, only seven of our control subjects were 40 years old or more, with a range of 41 to 62 and a mean age of 50 years. Five (71.4 per cent) of these persons were normal reactors, and two (28.6 per cent) were normal hyperreactors. No definite conclusions can be drawn from such a small group but it should be pointed out that the percentage of hyperreactors in regard to the diastolic blood pressure response is the same in the younger and older control subjects in this study. This does not support Russek and Zohman's[9] theory that vascular hyperreaction is a normal occurrence in persons in the older age group.

Effect of Severity of Hypertension on Pressor Response to Cold. The reason for the smaller increase in blood pressure to the cold stimulus in persons with hypertension of group 1 before treatment than in those in group 2 is not clear. The progressively smaller response of blood pressure to cold before treatment from groups 2 to 4 is undoubtedly due to the fact that as the severity of hypertension increases, the peripheral vessels have become persistently narrowed and cannot constrict much more when the cold stimulus is applied.

The Ganglionic Blocking Drugs. In evaluating the effect of the antihypertensive agents on the cold pressor response of the hypertensive patients, it should be noted that the patients with the more severe hypertension received the ganglionic blocking agents, hexamethonium and pentapyrrolidinium. The combinations of protoveratrine and reserpine, and hydralazine hydrochloride and reserpine did not change the blood pressure response to cold in any way in

an interval of one to three weeks between tests. This again shows the consistency of the cold pressor test when repeated at varying intervals of time. The combination of hydralazine hydrochloride, protoveratrine and reserpine caused little change in the cold pressor response, although the diastolic response was slightly less during treatment.

Although the cold pressor response was not completely blocked in any patient, the ganglionic blocking agents definitely diminished the response of blood pressure to cold. It seems that when hydralazine is combined with the hexamethonium ion, the combination not only lowers the basal pressure but also the pressor response to cold, although it is possible that this depression is entirely due to hexamethonium. The depression of the cold pressor response by the ganglionic blocking agents demonstrates that the efferent pathway of the cold pressor response is neurogenic and via the sympathetic nervous system. This finding is in agreement with those of other investigators.[10]

The diminution of the pressor response to cold by the ganglionic blocking agents is of significant clinical importance. The hypertensive patient, during his normal daytime activities, has a blood pressure closely approximating that of the maximal blood pressure during the cold pressor test. His blood pressure decreases to basal levels only when he is at rest in the supine position. The ganglionic blocking agents cause a decrease of the basal blood pressure and also depress the pressor response to cold and therefore the maximal pressure during the cold pressor test. This suggests that the patient's blood pressure during the average day's activity is less than it would be if antihypertensive agents which do not depress the cold pressor response were used in treatment of the hypertension. This is well shown in table 4. The patients treated with hexamethonium and hydralazine, for example, had an average maximal blood pressure of 246.9/137.4 mm. whereas during treatment it was only 184.8/90.4 mm. They had the most severe hypertension of any group in our study, as shown by the basal and maximal pressures before treatment. The maximal pressure of the patients in response to the cold stimulus during treatment with protoveratrine and reserpine (the mildest hypertensive patients in this study) was 212.5/102.6 mm. Although the resting pressure during treatment was somewhat lower than that of the patients treated with hexamethonium and hydralazine, the maximal pressure after the cold stimulus was significantly higher.

In general, findings are the same for the other groups shown in table 4; that is, the patients with severe essential hypertension treated with hexamethonium or pentapyrrolidinium had maximal pressures in response to the cold stimulus during treatment lower than or almost equal to those of the patients with milder hypertension treated with medicaments which did not decrease the cold pressor response. Also, table 4 shows that during treatment with the ganglionic blocking agents the maximal blood pressure in response to the cold stimulus was lower than, or equal to, the pretreatment basal pressures, whereas in the group receiving the other combination of drugs the maximal pressure approximated the pretreatment basal blood pressure or was much higher than the pretreatment basal pressure. This observation again shows the advantage of the ganglionic blocking agents in lowering blood pressure over other antihypertensive drugs.

Ideal Time to Determine Maximal Response to Cold Pressor Test. The results obtained in our measurements of the time to reach maximal blood pressure show that when the cold pressor test is done clinically by the indirect method, the blood pressure reading most likely to give the true maximal blood pressure should be made between 50 and 60 seconds after immersion of the hand in the ice water. In this study the maximal blood pressure very rarely occurred less than 50 seconds after the hand was immersed in the cold water.

Pulse Rate. The minimal rise in pulse rate during the cold pressor tests in this study is in agreement with observations of others.[2, 11] The increase is most likely to be secondary to the painful cold stimulus. A rise in pulse rate might be expected to occur immediately before immersion of the hand in ice water, while the technician is stirring the ice and removing it

from the container. At this time, the patient realizes that the cold stimulus is about to be applied, and some anxiety with a secondary increase in pulse rate may be expected. The fact that the pulse rate did not change between the time of the "random" pulse reading and the readings immediately before the cold pressor test suggests that there is practically no psychic factor involved in the cold pressor response.

Summary

Three cold pressor tests were performed at intervals of 15 minutes between each test on 65 normotensive and 60 hypertensive persons and the study was repeated on some of the control subjects in from 1 to 5 months and all of the hypertensive patients in about three weeks. In this study, the blood pressure was measured by the direct arterial method. The cold pressor test so performed proved a reliable index of vasomotor reactability, both of normotensive and hypertensive persons. Repetition of the test at short and long intervals yielded consistently constant responses of blood pressure for each person. The response did not seem to change with age, although only a small number of patients of older age were included in the control group.

The time between immersion of the hand in ice water and the maximal blood pressure was between 50 and 60 seconds in most of the control subjects and patients with essential hypertension. Therefore, the indirect reading most likely to give the true maximal blood pressure should be made at this time.

The cold pressor response was considered abnormal (1) if the increase in the diastolic blood pressure in response to cold was 15 mm. Hg or more and (2) if the maximal diastolic blood pressure ("ceiling" blood pressure) was 85 mm. Hg or more by the direct arterial method of recording blood pressure (90 mm. Hg or more if measured by the indirect method). Subjects with normal basal blood pressure whose diastolic blood pressure rose more than 15 mm., but whose maximal diastolic pressure was less than 85 mm. by direct measurement, were included in the normal reactor group. With these criteria, 46 (70.8 per cent) of the 65 control subjects were considered to be "normal reactors" and 19 (29.2 per cent) "normal hyperreactors."

The 60 patients with essential hypertension were studied before treatment was begun and while under treatment of the hypertension in order to evaluate the effect of various antihypertensive drugs on the cold pressor response. The response of their blood pressures to cold before treatment was uniformly greater than that of the control subjects except among those with the most severe hypertension. It is likely that the vessels of the latter could not constrict more under the added stimulus of cold, since they were already maximally constricted.

The ganglionic blocking agents, hexamethonium and pentapyrrolidinium, markedly depressed the cold pressor response and this observation appeared to be clinically significant. Hydralazine hydrochloride in combination with hexamethonium possibly aided in the depression of the pressor response to cold. Protoveratrine, reserpine and hydralazine in various combinations had no effect on the cold pressor response.

That the load placed on the heart by activity during treatment was greater in the less severely hypertensive patients than in those with severe hypertension is suggested by the fact that the severely hypertensive patients, who were treated with ganglionic blocking agents, had reduction of basal pressure and cold pressor response, and hence lower maximal pressure during activity, than did the milder hypertensive patients, who were treated with the other drugs. Thus, the ganglionic blocking agents would appear to have a clinical advantage over the other agents.

Summario in Interlingua

Le reaction del tension sanguinee a stimulation per frigido esseva registrate tres vices a intervallos de 15 minutas in 65 subjectos normotensive e in 60 patientes con hypertension essential tanto ante como etiam durante le tractamento con drogas antihypertensive. Le tension arterial esseva registrate directemente ab le arteria radial. Super le base de differentias in le responsas del individuos in le gruppo de controlo, le criterios de normo- e hyperreactivitate esseva modificate. In le patientes con

hypertension essential, agentes ganglioblocante produceva un marcate reduction del responsa a stimulation per frigido, sed varie combinationes de hydralazina, protoveratrina, e reserpina habeva nulle tal effecto.

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Blood Pressure Responses to the Valsalva Maneuver in Cardiac Patients with and without Congestive Failure

By WALTER E. JUDSON, M.D., J. D. HATCHER, M.D., PH.D. AND ROBERT W. WILKINS, M.D.

Compensated cardiac patients, like normal subjects, on performing the Valsalva maneuver show a decrease in systolic, diastolic, and pulse pressures during the blowing effort and a characteristic hypertensive overshoot after the release of the strain. Cardiac patients in congestive failure show the "failure response" with a maintenance of the systolic, diastolic, and pulse pressures during the expiratory strain and an absence of the overshoot afterwards. Experimental and clinical observations in patients indicate that this "failure response" is due to elevation of the right ventricular diastolic pressure, which interferes with the normal obstruction of venous return during the blowing effort of the Valsalva maneuver.

IN 1942, during studies in this laboratory on aviation medicine, particular attention was given to the Valsalva maneuver, which is capable of producing profound changes in the circulation, notably lowering of the arterial pressure associated with "blackout."[1] A clinical counterpart, so called "laryngeal epilepsy" or better, "tussive syncope," was also found to occur during paroxysmal coughing in persons with chronic pulmonary disease.[2] In 1947 attention was called to the usefulness of the Valsalva test in estimating the vasomotor reactivity of the sympathetic nervous system and especially in evaluating the effectiveness of surgical sympathectomy[3] or the administration of adrenergic blocking agents[4] in lessening this reactivity. Recently, during studies on the circulatory effects of ganglionic blocking agents in patients with cardiac decompensation,[5] it was found that the Valsalva responses of patients in congestive failure are abnormal. The purpose of this paper is to describe in detail the Valsalva responses of various types of cardiac patients with and without congestive failure.[6]

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MATERIAL AND METHODS

The control subjects had either normal or elevated arterial blood pressure but no evidence of congestive heart failure. The compensated cardiac patients were relatively free of symptoms and had normal peripheral venous pressures and circulation times. The patients with congestive heart failure had either decompensation of both ventricles or isolated failure of the right or left ventricle. The group of patients with congestive failure included patients with hypertensive, rheumatic, coronary (arteriosclerotic), or congenital heart disease, constrictive pericarditis, cor pulmonale, or arteriovenous fistula. Expiratory ("blowing") pressure, right atrial, right ventricular, pulmonary arterial, and systemic arterial pressure (above atmospheric) were recorded with electromanometers* and recorded by a direct-writing oscillograph. The standard Valsalva maneuver was performed by having the subject, who was in the supine position, take a full inspiration and exhale forcibly for 10 seconds at a pressure of 40 to 60 mm. Hg against a fixed resistance.

RESULTS

1. Blood Pressure Responses to the Valsalva Maneuver in Normal Subjects

The characteristic blood pressure responses during and immediately after the Valsalva maneuver in a normal subject are shown in figure 1. With the start of the expiratory strain the pulmonary arterial pressure increased, along with a transient rise in systemic arterial pressure. Then, with the maintenance of the strain, systemic arterial pressure fell (usually

* Sanborn Co., Cambridge, Massachusetts.

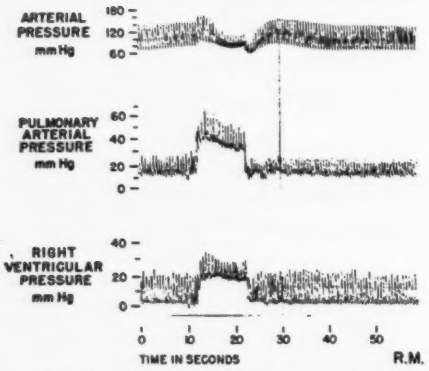

FIG. 1. Characteristic blood pressure responses to the Valsalva maneuver in a normal subject. With the strain a decrease in pulse pressure occurs and after its release a hypertensive overshoot appears.

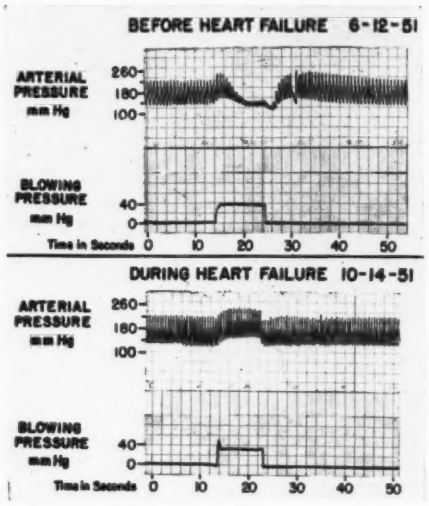

FIG. 2. The blood pressure responses to the Valsalva maneuver before and during congestive failure in a patient (J. P.) with hypertensive cardiovascular disease. In the upper tracing (before onset of heart failure) the normal blood pressure responses to the Valsalva maneuver are observed. In the lower tracing (during severe congestive failure) the typical "failure" blood pressure responses to the Valsalva maneuver are present. During the expiratory effort the pulse pressure shows no reduction, and after the release of the strain no hypertensive overshoot occurs.

systolic more than diastolic) presumably as a result of obstruction of venous return to, and reduction in stroke volume of, the heart. Similar decreases in the pulmonary arterial and right ventricular pressures occurred during the expiratory effort. As the strain was continued, leveling or even a slight rise of the systemic diastolic pressure often appeared, but with continued reduction of the pulse pressure. With the release of the strain, and of the high intrathoracic pressure that had been supporting the systemic arterial pressure, there was an immediate further transient fall in blood pressure followed by the quick appearance (within a few seconds) of a more or less marked overshoot, apparently due to a sudden increase in cardiac output in the face of a generalized vasoconstrictor response to the previous hypotension.

2. Blood Pressure Responses to the Valsalva Maneuver in Patients with Congestive Failure

The blood pressure responses to the Valsalva maneuver in a patient before and after the onset of acute congestive failure of the "low output" type are shown in figure 2. During cardiac decompensation (the lower section) the blood pressure responses to the Valsalva maneuver were strikingly different from those observed before the development of congestive failure. With the onset of the expiratory strain there was the usual prompt rise in arterial pressure, but there was a maintenance of the full pulse pressure without the normal decrease of systolic or diastolic pressure during the entire period of the expiratory effort.

The blood pressure response to the Valsalva maneuver in another patient during and after recovery from heart failure are illustrated in figure 3. During congestive failure (upper section), with the expiratory effort of the Valsalva maneuver the systemic arterial pressure rose immediately but the pulse pressure remained at control levels. Even when the maneuver was continued for a period longer than 10 seconds the pulse pressure decreased only very slightly, and with the release of the strain, the arterial pressure did not fall significantly below control levels. Nor was there any overshoot of arterial pressure to indicate a vasoconstrictor response or a sudden increase in the output of the left ventricle. The lower tracings in figure 3 show the blood pressure responses during the Valsalva maneuver when the patient

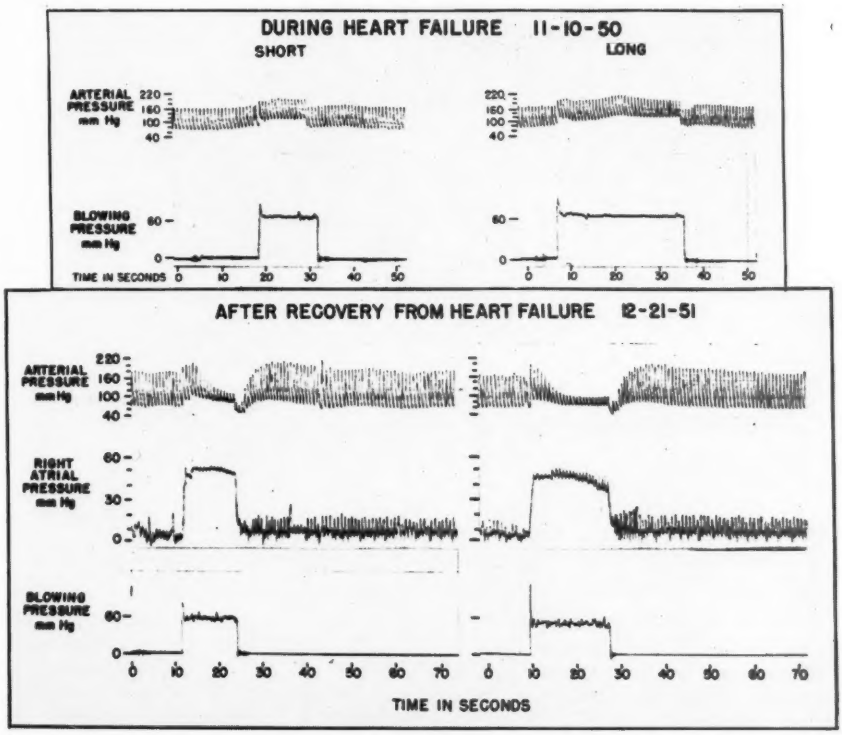

FIG. 3. The blood pressure responses to the Valsalva maneuver during and after recovery from congestive failure in a patient (J. B.) with arteriosclerotic heart disease. The upper tracing shows the maintenance of the pulse pressure during both a short and long expiratory effort and the absence of a post-straining overshoot during heart failure. The lower section is a record of the blood pressure responses to the Valsalva maneuver after treatment and recovery from heart failure. The pulse pressure decreases normally during the blowing effort, and the hypertensive overshoot is now present. The central venous pressure after treatment is normal.

had recovered from congestive failure. The right atrial pressure and the circulation times were normal. The blood pressure responses to the Valsalva test were now strikingly different from those found during congestive heart failure and resembled the normal responses.

3. Effects of Changes in Effective Blood Volume on Valsalva Responses in Patients with Congestive Failure

(*a*) *Venous Congestion of the Extremities or Venesection.* The application of venous congesting cuffs on the thighs, or the completion of a sizable venesection, in some patients with moderately severe congestive failure modified the blood pressure responses to the Valsalva maneuver, and made them resemble those occurring in normal individuals. In the upper section of figure 4 are shown the previously described typical "failure" responses to the Valsalva maneuver in patient J. B. both during a short, and a more prolonged, expiratory strain performed in the supine position. When blood was trapped in the extremities by inflating venous congesting cuffs on the thighs either in the horizontal position or during tilting into the upright position (75 degrees) the blood pressure responses to the Valsalva maneuver were found to be more normal. As shown in the lower section of figure 4, with the maintenance of the strain there was a reduction in arterial pressure (mainly systolic) and with the release of the strain a transient fall in systemic pressure followed by a rapid recovery

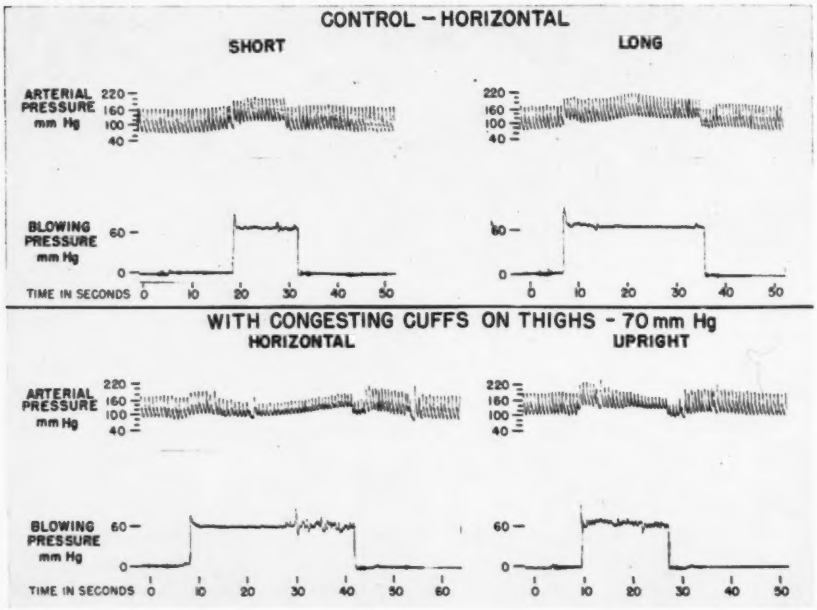

FIG. 4. The effects of trapping of blood in the extremities by venous congesting cuffs on the thighs on the arterial blood pressure responses to the Valsalva maneuver in a patient (J. B.) with arteriosclerotic heart disease and congestive failure. In the upper tracings the "failure" responses of the blood pressure are seen. In the lower tracings the application of congesting cuffs and the upright position are observed to modify the blood pressure responses (decrease in the pulse pressure during the strain and the appearance of overshoot after its release) so that they resemble those of the normal subject.

and a slight overshoot. In certain other patients with congestive failure, usually those with more severe types, venous congestion of the limbs did not alter significantly the pattern of the blood pressure responses.

(*b*) *Rapid Infusions of Large Volumes of Whole Blood or Hypertonic Saline Solution.* In a series of experiments in which large volumes of whole blood (varying from 600 to 1240 cc.) were infused within 6 to 12 minutes into normal or anemic individuals, the blood pressure responses to the Valsalva maneuver were observed to change from the normal to the "failure" pattern while the blood pressures in the right side of the heart rose. In the upper section of figure 5 the control normal Valsalva responses are shown. After the rapid infusion of 1240 cc. of whole blood, an abnormal or "failure" type of response appeared. When venous congesting cuffs were *then* inflated on the thighs the blood pressure responses to the strain resembled more closely the control pattern. When the cuffs were suddenly released the Valsalva responses again resembled those seen in patients with congestive failure. Fifteen minutes later the pattern of the blood pressure responses to the Valsalva maneuver had reverted to normal. Similar observations were made also in acute animal experiments.

4. Effects of Different Types of Heart Disease with and without Congestive Failure on the Valsalva Responses (Table 1)

The blood pressure responses to the Valsalva maneuver were graded in patients with various types of valvular and nonvalvular heart disease both with and without congestive heart failure. Uniformly, the degree of the "failure response" to the Valsalva maneuver bore no relation to the type of heart disease but varied with the severity of congestive failure as judged by the usual clinical criteria. Thus in patients with mi-

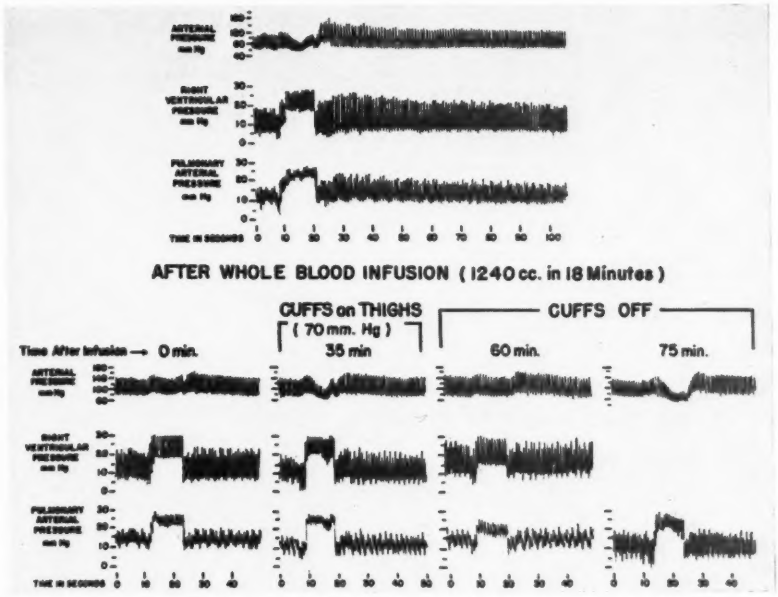
AFTER WHOLE BLOOD INFUSION (1240 cc. in 18 Minutes)
CUFFS on THIGHS
(70 mm. Hg)
CUFFS OFF
Time After Infusion → 0 min.
35 min
60 min.
75 min.

FIG. 5. The effects of altering acutely the effective blood volume on the blood pressure responses to the Valsalva maneuver in a patient (W. A.) with posthemorrhagic anemia without heart failure. The upper tracing shows the normal blood pressure responses. In the lower tracings, immediately after the infusion of 1240 cc. of whole blood, the "failure" type of responses are observed. With maintenance of venous congestion of the lower extremities the blood pressure responses return towards normal. Immediately after the release of the congesting cuffs on the thighs the blood pressure responses resemble the "failure" pattern. However, after a longer interval has elapsed the blood pressure responses are now similar to the normal control pattern.

tral stenosis a decrease in the pulse pressure occurred during the blowing effort and was followed by an overshoot when there was no congestive failure (fig. 6); whereas the pulse pressure was regularly maintained with virtually no overshoot when there was congestive failure. On the basis of hemodynamic data obtained from these patients and to be reported separately,[7] it may be stated that the pattern of the Valsalva response found in any patient could be correlated only with the degree of failure of the right ventricle and not with the degree of narrowing of the mitral valvular orifice, the severity of the pulmonary arteriolar disease or vasoconstriction, or the altered cardiodynamic responses to exercise.

In one patient with isolated aortic stenosis uncomplicated by congestive failure the overshoot of the blood pressure in the pulmonary and brachial arteries was grade IV and was unusually prolonged. This response was most remarkable in view of the fact that at operation the systolic pressure gradient between the aorta and the left ventricle was 100 mm. Hg and the valve size was estimated with a dilator to be less than 0.5 cm.[2]

In patients studied with isolated left ventricular failure (as shown by measurement of elevated "pulmonary capillary" pressures and normal right ventricular end-diastolic pressures during cardiac catheterization) the blood pressure during the Valsalva maneuver was found to decrease normally. However, there was a diminished or absent poststraining hypertensive overshoot. With combined left and right ventricular failure the blood pressure responses during the Valsalva maneuver were similar to those described for other patients in congestive failure.

Patients with cor pulmonale without congestive failure showed the usual decrease in pulse pressure during the expiratory effort but

TABLE 1.—*Valsalva Responses in Various Cardiac Patients*

Diagnosis	No. of Patients	Clinical* Classification	Pulmonary Artery		Brachial Artery	
			Decrease in Pulse Pressure	No. & Grade of "Overshoots"†	Decrease in Pulse Pressure	No. & Grade of "Overshoots"†
A. Low Output						
I. R.H.D.						
a. M.S.						
i. Without failure	2	I	2	2 (III)	2	2 (III)
	5	II	4	1 (I), 2 (II), 1 (III)	4	1 (I), 2 (II), 1 (III)
	5	III	5	2 (II)	5	3 (I), 1 (II), 1 (III)
	4	IV	3‡	2 (II)	4	2 (II), 1 (IV)
ii. With failure	8	III	2	3 (I)	1‡	3 (I), 1 (II)
	3	IV	0	0	0	0
b. A.S. (without failure)	1	III	1	1 (IV)	1	1 (IV)
c. M.I. with aneurysmal dilatation of l. atrium	3	IV	0	0	0	0
d. Multiple V.H.D. with failure	4	III	0	0	0	0
	4	IV	1	0	1	0
II. H.C.V.D. and/or A.S.H.D.						
i. L.V. failure	2	II	2	0	2	1 (I)
	3	III	3	0	3	0
ii. L.V. and R.V. failure	7	III	3‡	0	3‡	2 (I)
	2	IV	0	0	0	0
III. Congen. H.D.						
i. Without failure						
(a) Isolated P.S.	1	I	1	1 (I)	1	1 (I)
(b) I.A.S.D.	1	I	1	1 (I)	1	1 (II)
ii. With failure						
(a) I.A.S.D.	2	III	0	0	0	0
(b) Tetral. Fallot	1	II	0	0	0	0
(c) Eisenmenger's complex	1	II	1	0	1	0
IV. Constrict. pericard. (with fail.)	1	IV	0	0	0	0
B. High Output						
I. Cor pulmonale						
i. Without failure	7	II	7	1 (II)	7	1 (II)
	1	III	1	1 (II)	1	1 (II)
ii. With failure	3	III	0	0	3‡	0
	3	IV	0	0	2‡	0
II. Anemia (without failure)	6	I	6	2 (I), 3 (II), 1 (IV)	6	1 (I), 2 (II), 1 (III), 2 (IV)
	2	II	2	2 (II)	2	2 (II)
III. A-V fistula (with failure)	1	III	0	0	0	0

* Functional classification—New York Heart Association.

† Grading of overshoot based on Wilkins' classification.[3]

‡ Slight decrease in systolic pressure.

Abbreviations:

R.H.D. = Rheumatic heart disease
M.S. = Mitral stenosis
A.S. = Aortic stenosis
M.I. = Mitral Insufficiency
V.H.D. = Valvular heart disease
H.C.V.D. = Hypertensive cardiovascular heart disease
A.S.H.D. = Arteriosclerotic heart disease
L.V. = Left ventricular
R.V. = Right Ventricular
Congen. H.D. = Congenital heart disease
P.S. = Pulmonary stenosis
I.A.S.D. = Interatrial septal defect

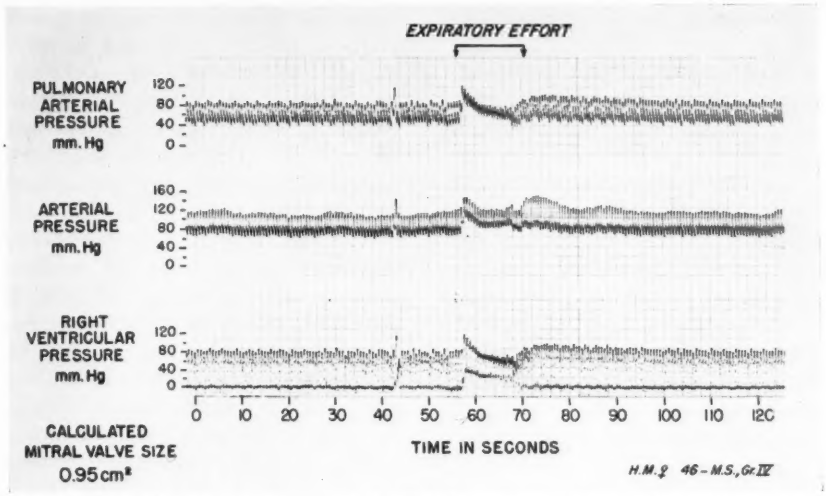

FIG. 6. The blood pressure responses to the Valsalva maneuver in a patient with severe mitral valvular stenosis and pulmonary vascular disease without right ventricular failure. Tracings show the decreases in the pulse pressure during the expiratory effort and the marked hypertensive overshoots that are similar to the responses observed in normal subjects.

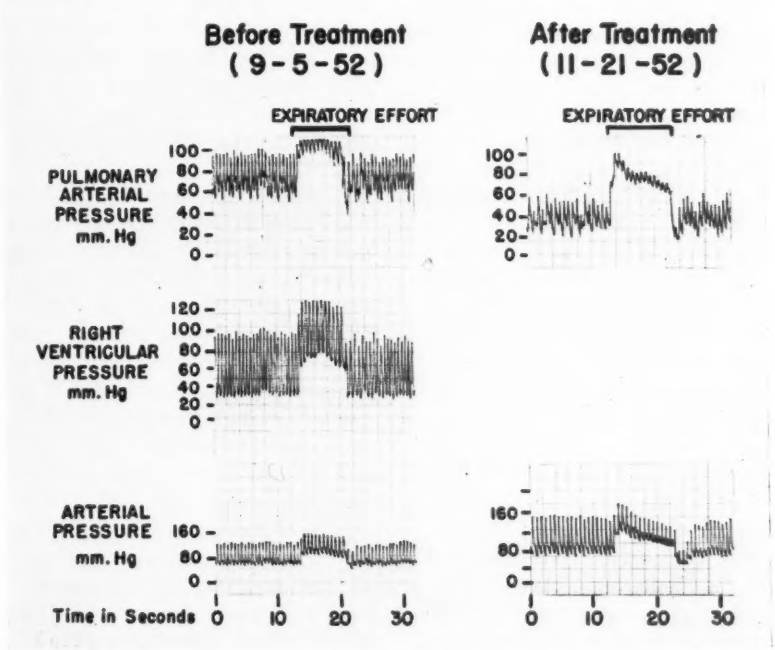

FIG. 7. The blood pressure responses to the Valsalva maneuver in a patient (M. A.) with cor pulmonale in congestive failure before and after treatment. Tracing on the left shows that the pulse pressure is maintained during the expiratory effort with no poststraining overshoot. After treatment and improvement in cardiac function the blood pressure responses are similar to those of normal subjects with a reduction of pulse pressure during the strain but with a persistent absence of the overshoot after the release of the blowing effort.

usually no overshoot in the blood pressures in the poststraining period. However, in the presence of an elevated right ventricular end-diastolic pressure the usual "failure response" to the Valsalva maneuver was observed (fig. 7).

One patient with an arteriovenous fistula who was in congestive failure had the typical "failure type" of blood pressure responses to the Valsalva maneuver, even though the cardiac output at rest was elevated and increased normally with exercise. Two years later after the repair of the fistula the patient had normal cardiodynamic measurements (with a lower cardiac output both at rest and in response to exercise) and blood volume, and a normal Valsalva response.

Discussion

The Valsalva "failure response" was uniformly observed in congestive heart failure whenever it was associated with moderate to severe elevations of the right ventricular end-diastolic pressure. It occurred in "low output" as well as in "high output" failure cases and regardless of the type of heart disease. The additional observations that the Valsalva "failure response" occurred after acute increases in circulating blood volume in normal subjects (and dogs) whose cardiovascular systems were fully capable of accommodating an increased input load by responding with only slight rises in central venous pressures and with no change or a slight increase in the cardiac output, suggests that impairment of cardiac function cannot be the sole explanation for the "failure response". Conversely, procedures designed to decrease the right ventricular end-diastolic pressure and/or effective blood volume in congestive failure without necessarily affecting greatly the resting level of cardiac output or the ability of the heart further to increase its output under stress, changed the "failure" pattern back toward those of a normal subject.

Studies by Stucki and coworkers[8] on the effect of the Valsalva maneuver on the circulation times (measured with P^{32}) from the antecubital and femoral veins to the brachial artery in normal subjects and in patients with congestive failure have shown that circulation times in normal subjects were uniformly increased during the Valsalva maneuver by an amount equivalent to the duration of the expiratory effort; whereas in patients with congestive failure the circulation times were retarded little if at all. Radiographic studies with Diodrast introduced into an antecubital vein or through a venous catheter into the inferior vena cava below the diaphragm showed that there is a damming and puddling of the Diodrast below the diaphragm or at the level of the first rib in normal subjects during the Valsalva maneuver, but a continuance of venous flow, particularly from below the diaphragm, in patients with congestive failure. These observations suggest that in patients with congestive failure the performance of the Valsalva maneuver does not impede normally the venous return to the right atrium.

The frequent diminution or absence of the normal poststraining hypertensive overshoot in patients with isolated ventricular failure, even when the pulse pressure is reduced normally during the strain, suggests that impairment of left ventricular stroke output in response to increased filling after the Valsalva maneuver may influence the degree of overshoot in the systemic blood pressure. Thus, in patient J.B. (fig. 3), after recovery from heart failure and even with a relatively fixed cardiac-output response to exercise, the decrease in pulse pressure now occurring during the strain was followed by a more normal overshoot in the systemic blood pressure than occurred when he was in failure.

The pattern of the pulmonary arterial pulse pressure during the expiratory effort and subsequent pulmonary hypertensive overshoot parallels the changes in systemic blood pressure. Competency of the right ventricle and an ability to increase its stroke output does not seem to be a factor in augmenting the degree of the overshoot in the pulmonary artery, but it is important in determining a maintained pulse pressure during the blowing effort of the Valsalva maneuver. (Circulation times determined from within the pulmonary artery to the brachial artery during the strain of the Valsalva maneuver in normal subjects showed

no increase in the circulation time, indicating that the block to venous return was not in the pulmonary vascular bed or in the left side of the heart.)[8]

Goldberg and associates[9] have stated that the hypertensive overshoot and the accompanying bradycardia after the Valsalva maneuver do not occur in patients with tight mitral stenosis. Since in significant mitral stenosis the cardiac output may be normal or low at rest, but relatively fixed during exercise, the authors suggest that immediately after the blowing effort of the Valsalva maneuver, a damming of blood occurs behind the stenotic mitral orifice, which limits left ventricular filling and output, and that this accounts for the absence of the hypertensive overshoot in the systemic blood pressure. McIntosh and associates,[10] utilizing the dye-dilution technic to measure the cardiac output response in the poststraining or recovery phase of the Valsalva maneuver, found that some patients with severe mitral stenosis had an increase in cardiac output while normal subjects usually showed a decreased cardiac output. Since a hypertensive overshoot in the systemic blood pressure was frequently found in their studies of patients with severe mitral stenosis (as well as in those by ourselves and other authors[11]), they suggested that both an increase in cardiac output and an alteration in total peripheral vascular resistance were the more important factors responsible for the overshoot. Our own studies of the blood pressure responses to the Valsalva maneuver in patients with mitral stenosis indicate that neither the size of the mitral valvular orifice nor the relatively fixed cardiac output is an important determinant of the pattern of the blood pressure responses during the strain, or the overshoot after its release. We conclude that the preponderant factor influencing the blood pressure responses both during and after the Valsalva maneuver in these patients is the height of the right ventricular end-diastolic pressure, which reduces the venous blockage normally caused by the Valsalva test.

Most of the patients with cor pulmonale without failure showed the usual decreases in the pulse pressure during the expiratory effort but absent overshoots in the pulmonary artery and systemic blood pressure afterwards. All of these patients had elevations of their resting pulmonary arterial pressures, most of which were increased further during exercise with an increase in cardiac output. The reason for the failure of overshoots to occur in either the pulmonary or systemic arteries remains obscure. Elisberg and his associates[12] made similar observations in the systemic pressure in a few patients and attributed the lack of systemic blood pressure overshoot to a decrease in the size of the pulmonary vascular bed and its increased resistance to sudden alterations in flow. These speculations are not consistent with our concepts regarding the presence or absence of overshoots, since patients with the severest types of mitral stenosis and pulmonary vascular disease do have overshoots when they do not have congestive failure. In the cor pulmonale patients with right ventricular failure, the usual Valsalva "failure response" was observed.

The patient with a large arteriovenous fistula who was studied during and after recovery from congestive failure provides additional evidence that the height of the right ventricular diastolic pressure, and not the ability to increase the cardiac output, is largely responsible for the type of blood pressure responses observed during the blowing effort of the Valsalva maneuver and the hypertensive overshoot occurring after the cessation of the expiratory effort.

Summary

The systemic blood pressure responses to the Valsalva maneuver in normal subjects and compensated cardiac patients consist of reductions in systolic, diastolic, and pulse pressure during the blowing effort, followed by a hypertensive overshoot after the release of the strain.

In patients with congestive failure there is a "failure response" of the blood pressure to the Valsalva maneuver characterized by a maintenance of the pulse pressure during the straining effort, and an absence or reduction in the poststraining hypertensive overshoot. It is suggested that this "failure response" results primarily from elevation of the right ventricu-

lar end-diastolic and venous pressures and thereby interference with the normal obstruction of venous return (particularly from below the diaphragm) during the blowing effort of the Valsalva maneuver. In congestive failure venous return is maintained, as is cardiac output and pulse pressure. Hence there is no hypotensive stimulus for vasoconstriction. Therefore the normal poststraining hypertensive overshoot does not occur.

The "failure" type of blood pressure responses to the Valsalva maneuver may be made to resemble the normal pattern by acute reductions in effective blood volume. Conversely, rapid increases in the effective blood volume by infusions of whole blood or hypertonic saline solution may produce the "failure" pattern of blood pressure responses during the Valsalva maneuver in normal subjects. In both experiments the associated changes in the right ventricular end-diastolic pressure appear to be the main factor influencing the responses by altering the venous return, particularly from below the diaphragm, during the Valsalva blowing effort.

The pattern of the blood pressure responses to the Valsalva maneuver in patients with valvular heart disease is not correlated with the severity of the obstruction at the valvular orifice but rather with the degree of failure of the right ventricle.

The blood pressure responses to the Valsalva maneuver in patients with cor pulmonale without failure show the usual reduction in the pulse pressure during the expiratory effort but an absence of the hypertensive overshoot with the release of the strain.

Summario in Interlingua

In individuos normal e in compensate patientes cardiac, le experimento de Valsalva produce un responsa que consiste in un reduction del pressiones systolic, diastolic, e pulsar durante le effortio expiratori e in un excesso hypertensive post le relaxamento de ille effortio.

In patientes con dysfunctionamento congestive, le experimento de Valsalva resulta in un "responsa dysfunctional" del pression sanguinee. Iste responsa es characterisate per le mantenentia del pression del pulso durante le effortio expiratori e per le absentia o reduction del excesso hypertensive post ille effortio. Nos opina que le "responsa dysfunctional" resulta primarimente de un elevation del termino-diastolic e venose pressiones dexteroventricular e de un consequente disrangiamento del normal obstruction del retorno venose (specialmente ab le region infra le diaphragma) durante le effortio expiratori del experimento de Valsalva. In dysfunctionamento congestive le retorno venose es mantenite, como etiam le rendimento cardiac e le pression del pulso. Ergo il ha in iste condition nulle stimulo hypotensive de vasoconstriction, e ergo le normal excesso hypertensive post le effortio del experimento de Valsalva non pote occurrer.

Le typo "dysfunctional" del pression sanguinee in responsa al experimento de Valsalva pote esser fortiate a resimilar configurationes normal per medio de acute reductiones del effective volumine de sanguine. Inversemente, un rapide augmento del effective volumine de sanguine causate per infusiones de sanguine integre o de un solution salin pote resultar in le typo "dysfunctional" del responsa del pression sanguinee post le experimento de Valsalva mesmo in individuos normal. In ambe experimentos le associate cambiamentos in le termino-diastolic pression dexteroventricular pare esser le principal factor in determinar le responsa per alterar le retorno venose, specialmente ab le region infra le diaphragma, durante le effortio expiratori del experimento de Valsalva.

In patientes con cardiopathia valvular le configuration del responsa del pression sanguinee al experimento de Valsalva non es correlationate con le severitate del obstruction al orificio valvular sed plus tosto con le grado del dysfunctionamento del ventriculo dextere.

In patientes con corde pulmonal sin dysfunctionamento, le responsa del pression sanguinee al experimento de Valsalva monstra durante le effortio expiratori le usual reduction del pression pulsar sequite post le relaxamento del effortio per nulle excesso hypertensive.

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Studies of Circulation Time During the Valsalva Test in Normal Subjects and in Patients with Congestive Heart Failure

By Paul Stucki, M.D., J. D. Hatcher, M.D., Walter E. Judson, M.D. and Robert W. Wilkins, M.D.

Circulation times (P^{32} from the antecubital and femoral veins to a peripheral artery) and roentgenographic studies of the pattern of venous distribution of a radio-opaque substance (Diodrast introduced through a cardiac catheter into the axillary vein and the inferior vena cava below the diaphragm) have been performed during the expiratory effort of the Valsalva maneuver. In normal subjects the circulation times were increased by the duration of the expiratory effort and the Diodrast injections were stagnated in the veins outside the thoracic cavity. These effects were in striking contrast to those in patients with congestive failure in whom the circulation times were retarded only partially if at all and the Diodrast injections continued to flow freely towards the right atrium during the expiratory effort. Thus, in patients with congestive failure the Valsalva maneuver does not interrupt the venous return to the right atrium as it does in normal subjects.

IN 1949 durin studies on the circulatoryg effects of ganglionic blocking agents in patients with congestive heart failure (1) it was found that such patients have abnormal arterial pressure responses to the Valsalva test.[2, 3] In contrast to the normal subject who, after a brief initial rise in arterial pressure, has a fall in systolic, diastolic and pulse pressure during the straining period (fig. 1), the patient in congestive failure has a rise of systolic and diastolic pressure and a maintenance of pulse pressure throughout the expiratory effort (fig. 2). On relaxing the strain, the patient in congestive failure simply has a return of arterial pressure to control levels without the characteristic normal overshoot. This response pattern of the patient in congestive heart failure has been called the "failure response." Occasional patients in moderate, but not severe, congestive failure have an "intermediate failure response", showing less than normal decrease in pulse pressure during, and less than normal (or absent) overshoot of pressure after the strain (fig. 3). In a large group of cases all variations between the full "failure response" and the normal response are seen.

The purpose of the present paper is to report the effect of the Valsalva maneuver upon circulation times in patients with and without congestive heart failure. In addition, radioscopic Diodrast studies during the Valsalva maneuver in two patients are presented.

Methods

The Valsalva maneuver was performed by having the supine subject take a full inspiration and forcibly attempt to exhale for a certain period of time, usually 10 seconds, into a closed manometer at a pressure of 40 to 60 mm. Hg. The systemic arterial pressure was recorded continuously with a Sanborn electromanometer connected to an inlying needle in a brachial or femoral artery.

Circulation time was measured from an antecubital vein, a femoral vein, or both, to a brachial or femoral artery before and during the Valsalva test. In three patients a cardiac catheter was placed in the pulmonary artery and the circulation time was measured from the pulmonary artery to a brachial or femoral artery.

Approximately 30 microcuries of essentially car-

From the Robert Dawson Evans Memorial, Department of Clinical Research and Preventive Medicine, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

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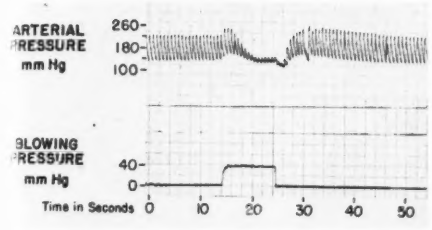

FIG. 1. Effect of the Valsalva maneuver on the blood pressure responses in a normal subject.

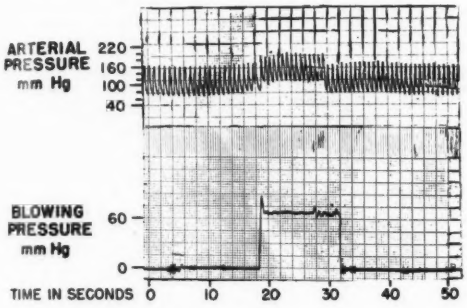

FIG. 2. Effect of the Valsalva maneuver on the blood pressure responses in a patient with congestive heart failure ("failure response").

rier-free radio-active phosphorus (P^{32}) as sodium phosphate in 1 to 2 cc. of physiological saline were injected intravenously. Arterial blood was then sampled from the intra-arterial needle at two second intervals. The first injection was made with the subject in the resting state in order to obtain a "control" circulation time. After 3 to 5 minutes a second injection of P^{32} was made at the onset of the Valsalva maneuver, care being taken that the P^{32} was not injected before the patient had started to strain.

From each two-second sample of arterial blood 0.2 cc. were pipetted into planchettes and dried overnight. The radioactivity of all samples from each patient was quantitated on the same day with a thin-window Geiger-Mueller tube (Tracerlab—TGC-2) and scaling circuit, sufficient counts being taken in each instance to reduce the error of counting to less than 2 per cent. The calculated counts per second were plotted against time in seconds. The curve thus obtained (fig. 4) showed a sudden rise of the radioactivity above the background count when the first P^{32} reached the site of sampling. The last point *before* a definite and continuous rise over the baseline was taken arbitrarily as the circulation time. In the same patient the circulation time by this method may be determined repeatedly to within two seconds. The method is entirely objective and was particularly advantageous in this study because it required no cooperation on the part of the patient.

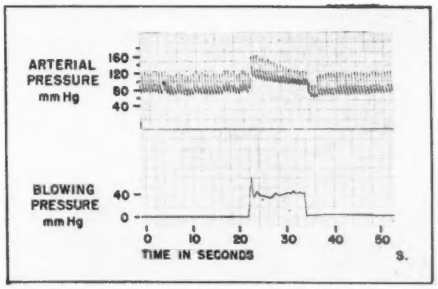

FIG. 3. The "intermediate failure response" of the blood pressure to the Valsalva maneuver in a patient with recent and mild congestive heart failure.

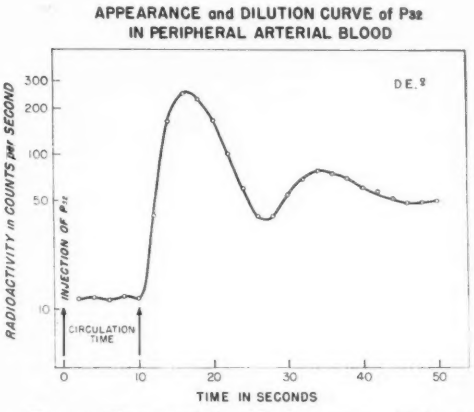

FIG. 4. Characteristic dilution curve (P^{32}) obtained for determining circulation time.

In two patients 10 cc. of a 30 per cent Diodrast solution were injected through a cardiac catheter into the inferior vena cava below the diaphragm (in one also in the axillary vein) during the Valsalva maneuver. X-ray films of the abdomen and thorax were taken at different intervals after the beginning of the maneuver.

RESULTS

The circulation times of the subjects with normal Valsalva responses are given in table 1. It can be seen that in all cases the circulation times were greater during the Valsalva maneuver than during the control period. In other words, there was a definite delay of the circulation time as a result of the strain. Thus, in the subjects who strained for a 10-second period, the delay from the arm (antecubital vein) as well as from the leg (femoral vein) averaged 10 seconds, ranging between 8 and

TABLE 1.—*Summary of Circulation Time (P^{32}) from Antecubital and Femoral Veins to Peripheral Artery Before and During Valsalva Maneuver in Patients without Congestive Heart Failure*

Patient	Diagnosis	Antecubital Vein to Peripheral Artery					Femoral Vein to Peripheral Artery					Blood Pressure Response to Valsalva Man.
		Circ. Time Control (secs.)	Blowing Time (Valsalva Maneuver) (secs.)	Circulation Time during Valsalva (secs.)	Delay of Circ. Time during Valsalva (secs.)	% Delay in Circ. Time during Valsalva (%)	Circ. Time Control (secs.)	Blowing Time (Valsalva Man.) (secs.)	Circ. Time during Valsalva (secs.)	Delay of Circ. Time during Valsalva (secs.)	% Delay in Circ. Time during Valsalva (%)	
A. S.	Psychoneurosis	14	10	22	8	80	12	10	22	10	100	N†
J. T.	Normal	14	10	24	10	100	12	10	22	10	100	N
G. G.	Duodenal ulcer	12	10	20	8	80	12	10	22	10	100	N
R. M.	Essential hypertension	14	10	26	12	120	10	10	22	12	120	N
A. M.	Bronchial asthma; essential hypertension	16	10	26	10	100	14	10	24	10	100	N
J. B.	A.S.H.D. compensated	20	18	38	18	100	20	19	28	8	41 (80)*	N
F. G.	A.S.H.D. compensated old myocardial infarction	8	10	18	10	100	—	—	—	—	—	N
E. D.	Essential hypertension	—	—	—	—	—	10	16	22	12	75 (100)*	N

* Calculated for a blowing time of 10 seconds.
† N = normal.

12 seconds. In subjects E. D. and J. B., who strained for longer than 10 seconds, there was also a definite delay. Percentagewise the delay in these two subjects amounted to 100 per cent of the straining period measured from the arm, but to only 41 to 75 per cent from the leg. However, calculated on the basis of 10 seconds, the delay from the leg was at least 80 per cent, as in the other normally responding subjects. This, as well as previous experience, has convinced us that a Valsalva test with a 10-second straining period is about optimal for producing blockage of the circulation in normal subjects. If the strain is prolonged beyond 10 seconds, the venous return, particularly from below the diaphragm, apparently may break through the blockade (see "Discussion").

Table 2 gives the results obtained in patients with various types of "failure response." The control circulation times in these patients were, with three exceptions, greater than normal. A Valsalva maneuver of 10 seconds produced a variable delay of the circulation time when measured from the arm to a peripheral artery, ranging between 0 and 100 per cent of the actual straining time. On the average, the delay was considerably less than in the normal group shown in table 1. However, there were two patients who had a 100 per cent delay of the arm vein to artery time as did the normal subjects. It is interesting that both these patients had a normal control circulation time. Both had undergone mitral valvuloplasty with considerable improvement of their circulatory status.

The results measured from a femoral vein to a peripheral artery in the failure group were much more consistent than from the antecubital vein. With one exception the Valsalva maneuver produced no significant delay of the leg to artery time; i.e. the delay did not exceed 20 per cent of the blowing period, although in some patients it did cause a delay in the arm to artery time.

The patient G. G. (tables 1 and 2) deserves special comment. Clinically this man had a normal cardiovascular status. After rapid infusion of 650 cc. of whole blood within eight minutes this patient had a moderately elevated right ventricular end-diastolic pressure of 8 mm. Hg and an increased arm-to-artery circulation time of 24 seconds. The Valsalva maneuver was then characterized by an abnormal "intermediate failure response". The delay in the arm to artery circulation time during the Valsalva maneuver was only 20 per cent of the

TABLE 2.—*Summary of Circulation Time (P^{32}) from Antecubital and Femoral Veins to a Peripheral Artery Before and During the Valsalva Maneuver in Patients with Congestive Heart Failure*

Patient	Diagnosis	Antecubital Vein to Peripheral Artery					Femoral Vein to Peripheral Artery					Blood Press. Resp. to Valsalva Man.
		Circ. Time Control (sec.)	Blowing Time (Valsalva Man.) (sec.)	Circulation Time during Valsalva (sec.)	Delay of Circ. Time during Valsalva (sec.)	Delay (Valsalva) of Blow. Time (%)	Circ. Time Control (sec.)	Blowing Time (Valsalva Man.) (sec.)	Circ. Time during Valsalva (sec.)	Delay Circ. Time during Valsalva (sec.)	Delay (Valsalva) of Blow. Time (%)	
J. K.	H.C.V.D. Cong. failure (r. & l.)	24	10	24	0	0	24	10	26	2	20	F*
C. L.	H.C.V.D. Cong. failure (r. & l.)	40	10	42	2	20	36	10	38	2	20	F
C. B.	A.S.H.D. Cong. failure (r. & l.)	32	10	38	6	60	24	11	26	2	18	F
A. G.	A.S.H.D. Cong. failure (r. & l.)	26	10	30	4	40	26	10	26	0	0	F
L. C.	R.H.D. M.S. Cong. fail.	24	10	26	2	20	24	10	26	2	20	F
A. Ls.	R.H.D. M.S. Postoper. valvuloplasty, cong. failure	10	10	20	10	100	12	10	18	6	60	F
C. G.	R.H.D. M.S. Clinically no cong. failure	10	10	14	4	40	16	10	18	12	20	I†
J. C.	R.H.D. M.S. Postop. valvuloplasty, cong. failure	12	10	24	12	120	—	—	—	—	—	F
G. G.	Duodenal ulcer. Right ventricular press. 29/8 mm. Hg after infusion of 650 cc. whole blood within 8 minutes.	24	10	26	2	20	—	—	—	—	—	I

* Failure.
† Intermediary.

blowing time, resembling that in patients with congestive failure. Seven days later, when he had recovered from the blood infusion, the control circulation time had returned to a normal value of 12 seconds and the arterial pressure response to the Valsalva maneuver was normal. In keeping with these findings the delays of circulation time during the maneuver from the arm and the leg were now 80 per cent and 100 per cent, respectively.

A similar experiment was carried out in a dog under Nembutal anesthesia. The Valsalva maneuver was performed by passive inflation of the lungs with a pressure of 40 mm. Hg for a 10-second period. The control circulation time from the femoral vein to the femoral artery was 8 seconds and the delay of the circulation time during the Valsalva maneuver was 100 per cent. After rapid infusion of 1650 cc. of saline within 15 minutes into the right auricle, the "control" circulation time was unaltered (8 seconds), but the Valsalva response had changed from normal to an "intermediate failure" type. There was now only a 40 per cent delay of the circulation time during the Valsalva maneuver.

Thus in a patient and in a dog, in whom the Valsalva response was changed from the normal to the intermediate type after large rapid intravenous infusions, the delay of the circulation time during the maneuver underwent corresponding changes from complete (normal) delay to less or none at all.

Table 3 gives the circulation times from the pulmonary artery to a peripheral artery before and during the Valsalva maneuver in one normal subject and in two patients with mild congestive failure who were studied after mitral

TABLE 3.—*Effect of Valsalva Maneuver on Circulation Times (P^{32}) from Pulmonary Artery to Peripheral Artery and from Antecubital and/or Femoral Veins to Peripheral Artery in Patients with and without Congestive Failure*

Patient	Diagnosis	Pulmonary Artery to Peripheral Artery					Antecubital and/or Femoral Veins to Peripheral Artery		Blood Pres. Resp. to Valsalva Man.
		Circ. Time Control (secs.)	Blowing Time (Valsalva Man.) (secs.)	Circ. Time during Valsalva (secs.)	Delay of Circ. Time during Valsalva		Delay of Circ. Time (Antecubital Vein to Periph. Art. during Valsalva) %	Delay of Circ. Time (Femoral Vein to Periph. Art. during Valsalva) %	
					(secs.)	%			
W. A.	Normal	8	10	10	2	20	—	—	N*
A. Ls.	R.H.D. M.S. Postop. valvuloplasty, cong. failure	6	10	6	0	0	100	60	F†
J. C.	R.H.D. M.S. Postop. valvuloplasty, cong. failure	8	10	8	0	0	120	—	F

* Normal.

† Failure.

FIG. 5. Roentgenogram taken 10 seconds after the injection of Diodrast solution through an intravenous catheter below the diaphragm in a patient with compensated heart disease (R. M.). The absence of any visible radio-opaque substance in the area below the diaphragm indicates that it has left the inferior vena cava and distributed itself in the general circulation.

FIG. 6. Roentgenogram taken of the same patient (R. M.) during the injection of Diodrast solution through an intravenous catheter below the diaphragm while the patient was performing the expiratory effort of the Valsalva maneuver. The radio-opaque material is now observed to be puddled below the diaphragm with none appearing above it suggesting venous obstruction at the level of the diaphragm.

FIG. 7. Roentgenogram taken of the same patient (R. M.) after the injection of contrast substance through a catheter into the right axillary vein during the Valsalva maneuver shows the pooling of the radio-opaque material in the veins outside, but not within, the thoracic cavity, indicating obstruction to the venous flow at this junction.

FIG. 8. Roentgenogram taken of patient I. K. with severe congestive failure four seconds after completion of the injection of Diodrast solution through a catheter below the diaphragm shows the presence of radio-opaque material both below and above the diaphragm.

valvuloplasty. None of these individuals showed a significant delay of the pulmonary to peripheral artery time during the Valsalva maneuver.

Figures 5 to 9 inclusive show the results obtained in two patients by Diodrast studies before and during the Valsalva maneuver. Patient R. M. had a moderately severe arterial hypertension but no elevation of the pulmonary arterial or right ventricular diastolic pressure at rest. He had a normal arterial pressure response, and a normal full delay of the circulation times during the Valsalva maneuver. With the patient resting quietly, 10 cc. of 30 per cent Diodrast were injected through a cardiac catheter into the inferior vena cava below the diaphragm over a period of 10 seconds. The roentgenogram (fig. 5) taken at the eleventh second after the beginning of the injection, showed no significant amount of radio-opaque material at the site of injection, indicating that the Diodrast had already left the vein at that time. There were only a few residual streaks of Diodrast adhering to the wall of the vein, giving a rather poor outline of the vessel.

Figure 6 shows the result obtained by injecting Diodrast solution in the same patient (R. M.) during the Valsalva maneuver. The contrast substance was given over an eight-second period, the roentgenogram taken at the eighth second. In contrast to figure 5, a large quantity of radio-opaque material can be seen in the inferior vena cava *distal* to the tip of the catheter, superimposed partially on the shadow of the spine. No contrast medium is detectable proximal to the catheter tip. The radio-opaque material obviously did not move upwards in the direction of the right heart during the whole period of the injection.

Figure 7 gives the result obtained when the

FIG. 9. Roentgenogram taken in the same patient, I. K., during the injection of the contrast medium through a catheter below the diaphragm while the expiratory effort of the Valsalva maneuver was being performed shows a similar distribution of the radio-opaque material above and below the diaphragm indicating an absence of any obstruction to venous flow.

Diodrast solution was injected through the catheter into the right axillary vein during the Valsalva maneuver in the same patient, R. M. The contrast substance is accumulated at the site where the vein enters the thoracic cavity, outlining clearly the venous network in the axilla. No radio-opaque material can be detected in the veins within the thoracic cavity.

Diodrast solution was injected similarly into the inferior vena cava of a patient in severe congestive failure (I. K., table 2). This patient had a markedly elevated control circulation time of 24 seconds, a "failure response" to the Valsalva maneuver and a delay of the circulation time during the maneuver of only 0 per cent and 20 per cent, respectively, from the arm and the leg. When 10 cc. of Diodrast solution were injected into the patient at rest over a six-second period and a film was taken at 10 seconds (fig. 8), the radio-opaque material was readily seen in the inferior vena cava both distal and proximal to the tip of the catheter with the head of the column just above the diaphragm. This was in contrast to the relatively quick disappearance of the contrast medium in the patient who was not in congestive failure, but was quite in keeping with the slow circulation time and the elevated right ventricular diastolic pressure in this patient.

When the injection was repeated *during* the Valsalva maneuver (injection over a period of six seconds), the roentgenogram taken at the fifth second revealed essentially the same pattern (fig. 9), i.e., the radio-opaque material could be detected distal and proximal to the catheter tip and passing just above the diaphragm towards the right heart. This was in striking contrast to the subject with a normal Valsalva response, in whom the Diodrast *remained* distal to the diaphragm and did not flow in the direction of the heart during the maneuver.

DISCUSSION

The results reported here indicate that in individuals with normal Valsalva responses the venous return from the arm and leg is blocked during a Valsalva maneuver for about a 10-second period. The data in table 3 also show that the circulation from the pulmonary artery to a peripheral artery is not blocked during the Valsalva maneuver. Identical results have been obtained by Matthes (4), using a different method. The Diodrast studies revealed that radio-opaque material deposited just outside the thoracic cavity does not flow in the direction of the right heart during a Valsalva maneuver in a normally responding subject.

Thus, direct and indirect evidence was obtained that the venous return is blocked during the strain of the Valsalva maneuver and that this causes a decrease in cardiac output and the consequent drop of the systolic, diastolic and pulse pressures. Thus, the theory originally forwarded by Buerger[5, 6] that a block of the circulation occurs in the pulmonary vascular bed during the Valsalva maneuver (due to an elevated intrapulmonary pressure which cannot

e overcome by the relatively weak right entricle) must be discarded. Indeed, Buerger imself abandoned it, at least partially, in the ter stages of his investigations of the Valsalva xperiment.[7]

It was not the primary purpose of the present udy to determine how long the circulation me can be delayed when a patient strains for nger than 10 seconds. Walz and Zimmermann[8] using a similar method with P^{32}) have reported irculation times from arm vein to arm vein in ve normal subjects who strained between 30 nd 40 seconds. All five individuals demonstrated a delay of 100 per cent of the blowing period. This was true for our patient, J. B. (table 1), who strained for 18 seconds (delay 100 per cent). The situation, however, seems to be different for the circulation times from the femoral vein. The two individuals who strained for 16 and 19 seconds, respectively, showed a delay of the circulation time during the Valsalva maneuver of only 12 and 8 seconds. As already mentioned it would appear that the venous return from the arm can be impeded more readily and for a longer period of time than that from the leg. Experience in this laboratory has shown that the most striking and pronounced blood pressure changes are usually obtained by having the subject strain for a period of about 10 seconds. The majority of subjects begin to have a return of arterial pressure toward control levels when the Valsalva maneuver is carried out for longer than 10 seconds.

In the patients with a "failure response" to the Valsalva maneuver the delay of the circulation time by the strain was definitely less than in the normal subjects. This was particularly true for the circulation time from the femoral vein, indicating that little or no block of the venous return from that area occurred during the Valsalva maneuver in these subjects. A similar situation was found for return from the arm vein; although in some patients the delay from that area was greater than from the femoral vein. As in the normal subject, it would appear that in patients with congestive failure, expiratory straining may impede venous flow from the arm more readily than from the leg. Thus, during the Valsalva maneuver the return from the inferior vena cava is apparently of greater importance than that from the superior cava in determining the type of arterial pressure response to the maneuver.

The fact that in subjects with a "failure response" the venous return to the right heart is not blocked from the femoral vein during the Valsalva maneuver and may not be even from the arm appears to explain the difference between the "normal" and the "failure" type of Valsalva response. In the latter the filling of the heart is maintained during the strain, at least to an extent adequate to insure that there is no, or only a partial, decrease of cardiac output and of systolic, diastolic, and pulse pressure in the peripheral arterial system.

Summary

The effect of the Valsalva maneuver on the circulation times from both the antecubital and femoral veins to a peripheral artery has been measured with P^{32} in normal subjects, compensated cardiac patients, and in patients with congestive failure.

In normal subjects and compensated cardiac patients the circulation times increase during the Valsalva maneuver by roughly the duration of the expiratory strain.

In patients with congestive failure the circulation times are not retarded, or are only partially retarded during the strain of the Valsalva maneuver.

Roentgenograms taken after the introduction of Diodrast solution through a venous catheter into the inferior vena cava below the diaphragm (or in the axillary vein outside the thoracic cavity) during the Valsalva maneuver indicate that in patients with congestive failure the expiratory effort of the Valsalva maneuver does not interrupt normally the venous return to the right atrium.

These observations on circulation time and the concentration and movement of the contrast substance (Diodrast) in the venous system suggest that the blood pressure responses during the Valsalva maneuver are determined by the height of the right ventricular end-diastolic pressure, which in-

fluences the venous return to the right side of the heart during the expiratory strain.

Summario in Interlingua

Le effecto del experimento de Valsalva super le tempore de circulation ab le venas tanto antecubital como etiam femoral usque a un arteria peripheric esseva mesurate per medio de P^{32} in individuos normal, in compensate patientes cardiac, e in patientes con dysfunctionamento congestive.

In individuos normal e in compensate patientes cardiac, le tempores de circulation se augmenta durante le experimento de Valsalva per grossiermente le duration del effortio expiratori.

In patientes con dysfunctionamento congestive le tempores de circulation non es retardate del toto o solo partialmente durante le effortio del experimento de Valsalva.

Roentgenogrammas facite post le introduction durante le experimento de Valsalva de un solution de Diodrast per un catheter venose a in le vena cave inferior infra le diaphragma (o a in le vena axillar al exterior del cavitate thoracic) indica que in patientes con dysfunctionamento congestive le effortio expiratori del experimento de Valsalva non interrumpe normalmente le retorno venose al atrio dextere.

Iste observationes in re le tempore de circulation e le concentration e movimento del substantia de contrasto Diodrast in le systema venose pare indicar que le responsas del pression sanguinee durante le experimento de Valsalva es determinate per le magnitude del termino-diastolic pression dexteroventricular que influe durante le effortio expiratori super le retorno venose al latere dextere del corde.

Acknowledgement

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Arteriosclerotic Occlusion of Cerebral Arteries: Mechanism and Therapeutic Considerations

By WALTER L. BRUETSCH, M.D.

The brains of 20 patients with cerebral arteriosclerosis have been studied with regard to the exact mechanism of occlusion of the arteries in encephalomalacia. The histologic material has convinced the author that the concept of "cerebral thrombosis" in its present wide application is erroneous; there is arterial occlusion but the mechanisms of its production, which are discussed, are not the usually accepted ones.

ARTERIOSCLEROSIS is responsible for approximately 90 per cent of all occlusive vascular diseases of the brain occurring after the age of 50. Its dramatic clinical expression is apoplexy. In four out of five instances of an arteriosclerotic stroke, the fundamental lesion is ischemia and in its extreme form softening (encephalomalacia) due to vascular obliteration, supposedly brought about by thrombosis. For this reason, the condition has been referred to as cerebral thrombosis. In the anatomic material of this study no histologic evidence of "thrombosis" was observed. The arterial occlusions were caused by other mechanisms.

The purpose of this study is to present the histologic alterations which lead to narrowing and at times to occlusion of the arterial tree in cerebral arteriosclerosis.

A review of the literature of the past 50 years reveals few investigations which have been devoted to this subject. Foix and Ley[1] in their excellent contribution on cerebral infarction in 1927 remarked that little if anything is found in classical neurologic text books on the exact anatomic state of the blood vessels in this condition. And this is true today.

In 1933 there appeared what is possibly the most comprehensive study dealing with arteriosclerotic changes of cerebral vessels in human material. The work was done by Wolkoff[2] under the guidance of Anitschkow,[3] who is known as the originator of experimental cholesterol atherosclerosis. The study emphasized the deposits of lipids in the wall of the arteries.

Anitschkow's hypercholesterolemic theory[3] is by far the most important single contribution to the understanding of arteriosclerosis, although his concept has not remained unchallenged. In recent years this approach has gained new impetus through the studies of Gofman and his colleagues,[4] and at present most research is being done by biochemists to the almost complete exclusion of the histologists.[5]

However, there are certain aspects of the problem which cannot be solved by the biochemical approach or by animal experimentation and which can be advanced only by histologic study of human material.

HISTOLOGY OF VASCULAR LESIONS

Broadly speaking, the human arteriosclerotic lesions in large arteries, such as the aorta, coronary arteries, and the vessels of the circle of Willis of the brain (fig. 1), and their immediate extensions, are predominantly fatty in type, due to an accumulation of cholesterol and other lipids in the arterial wall. In the small cerebral arteries, on the other hand, endothelial proliferation alone, without lipid deposits, produces occlusion. And in the smallest vessels, including the minute arterioles which give rise to the capillaries, hyalinization of the vessel wall, also called hyaline degeneration, is an

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FIG. 1. Basilar artery from a patient with severe cerebral arteriosclerosis. The grotesquely distorted vessel is completely occluded, and the customary diagnosis would be "thrombosis" of the basilar artery. Histologic analysis of serial sections reveals the occlusion to be the result of a huge deposit of lipid (A). The upper two-thirds (B) of the former lumen consist of connective tissue, containing in another level an area of bone marrow formation. In the occluding tissue there is then a gamut of connective tissue cells which have arisen from the mesenchyme and differentiated in various directions. This feature is unlike the change observed in an old organized thrombus. Toluidin blue stain.

FIG. 2. Hyalinization of arteriole from the putamen of the brain. The vessel wall is several times its normal thickness. At one side of the lumen (arrow) there is proliferation of endothelial cells, some of these exhibiting mitotic figures (see fig. 3). H.E. stain.

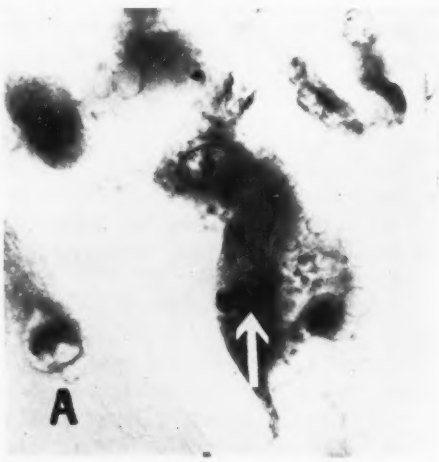

FIG. 3. Endothelial cell in the stage of mitosis. At A is the wall of the vessel. H.E. stain.

important feature of the vascular alterations in arteriosclerotic encephalomalacia. Hyalinization is often associated with thickening of the vessel wall, leading at times to complete obliteration of the lumen. In addition, there may be endothelial proliferation (figs. 2, 3). The obliterative changes of the small arteries and arterioles are the cause of the "little strokes."

In the large cerebral arteries a major factor which contributes to narrowing and occlusion is the deposition of lipids. In the small cerebral arteries the occlusion is the result of endothelial proliferation. Here the histologic features suggest clearly that the endothelium is primarily involved. However, in the large cerebral arteries endothelial and fibroblastic cell proliferation may also be of some, if not of greater, importance than the deposition of lipids in causing occlusion. The lipid deposits are often walled off from the remaining lumen by relatively huge layers of fibroblastic tissue. These so-called fibroblastic cushions appear to be much more than a mere reparative reaction to the "foreign body" material represented by the lipid. There is experimental evidence that there will be no formation of atherosclerotic plaques, despite a marked hypercholesterolemia, unless the tissue has the innate ability to react to lipid infiltration.[6]

ETIOLOGIC CONSIDERATIONS

Furthermore, the concept of Gofman and his coworkers[7] that certain classes of lipoprotein

nolecules (S_f 10-20) are closely associated with the development of atherosclerosis is difficult to substantiate in human cases. In a representative group of my patients with repeated arteriosclerotic strokes, the blood cholesterol and the lipoprotein levels (S_f 10-20 class), as determined by ultracentrifugal analysis, displayed little decisive change from a group of "normal subjects" of similar age. Barr[8] is of the opinion that these tests do not deviate with sufficient constancy to permit their practical use in the clinical diagnosis of atherosclerosis or of a tendency to its development.

It has been said many times that the degree of atherosclerosis increased parallel with the quality of nutrition, being most pronounced in countries with excessive nutrition, particularly of cholesterol. The North American diet is possibly the richest in cholesterol-containing food (eggs, milk, butter, cream, cheese, etc.), yet in European countries, for instance Italy, with diets much poorer in cholesterol, cerebral and coronary arteriosclerosis are also frequent diseases. Danish vital statistics,[9] like the statistics in the United States, rank cerebral apoplexy as the third commonest cause of death, following only coronary heart disease and cancer. These and other observations[10] are adding to the evidence which seems to indicate that a high cholesterol intake is not the all important factor in the causation of atherosclerosis.

Mechanism of Occlusion

This brings us back to the other alteration in the atherosclerotic plaque, namely, endothelial and later fibroblastic hyperplasia. One will have to ask the question: What causes the fibroblastic proliferation in the plaque? Some observers feel that the fibroblastic reaction is initiated by the lipid deposit, but in many instances one has the impression that new formation of connective tissue in the plaque has been suffocated rather than stimulated by the lipid. There is usually no tendency of fibroblasts to grow toward the lipid deposit in an attempt to organize it. The fatty substance seems to lie in the tissue in an inert manner. Even after the lipid deposit has been well organized and demarcated from the remaining lumen, the tendency toward fibroblastic activity continues in places where it serves no further purpose. These observations suggest that fibroblastic proliferation is most likely an important factor in atherosclerosis. In other words, as in the small cerebral arteries, in which endothelial proliferation is the basic feature, so in plaque formation of the larger arteries, involvement of the endothelial cells and of their close relatives, the fibroblasts, may be of paramount importance.

This view receives corroboration from the presence of what the author terms "embryonic foci of cellular proliferation" in the fibrotic part of the plaque. Such foci of cellular proliferation are often located in the surface of the fibrotic cushion, being in contact with the remaining lumen where they lead to further extension of the fibroblastic obliteration of the artery. In these areas there is no normal endothelial lining but, instead, there is a wall of loosely arranged cells, from 1 to 15 cells deep, consisting of a variety of cellular elements. The cells may be young fibroblasts or lymphocytes and particularly Maximow's undifferentiated mesenchymal cells, or a mixture of these and of still other cell types. Amitotic cell division of some of these cellular elements is often present. Such foci can be considered to

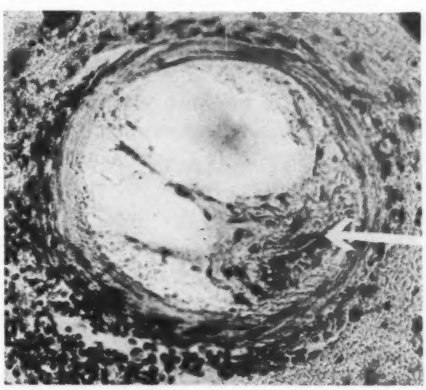

Fig. 4. Small cerebral artery. "Focus of embryonic cellular proliferation" (arrow), sending through the lumen a syncytial-like tongue of cytoplasm containing minute hyperchromatic nuclei. In the perivascular space is an area of lymphocytic cells. Toluidin blue stain.

be in an embryonic state, which may erupt at any time and lead to further fibroblastic growth.

The reason why the "embryonic foci of cellular proliferation" (fig. 4) have not been described previously is because they are not obvious; they consist of relatively few cells. They become particularly evident in rapidly progressive cases of atherosclerosis and in vessels which are fixed in alcohol, embedded in celloidin, and stained with toluidin blue or one of the other basic anilin dyes. These cellular foci are inconspicuous, because fibrotic narrowing of the lumen is in most instances an exceedingly slow process, going on over many years. For this reason, easily perceptible changes cannot be expected.

Therapeutic Considerations

In the beginning of this paper it was mentioned that the now prevailing concept of thrombosis in arteriosclerotic cerebral vascular occlusion, in its present wide application, is incorrect. It is true that gross examination of the large cerebral arteries may disclose a blood clot adhering to the vessel wall, but histologic examination fails to show lamination or any other characteristics of a true thrombus. The reason why a column of blood over a limited distance adheres to the vessel wall, suggesting a thrombus, is often due to a localized and rapid proliferation of endothelial cells which entangles red cells and thus forms an occluding mass. This observation goes well with the fact that no general disturbance of the coagulation mechanism has been demonstrated in patients with arteriosclerosis. It also explains the poor results of anticoagulants in the treatment of arteriosclerotic cerebral infarction.[11]

The reason for the poor results of anticoagulants has just been given. The use of a low cholesterol-low fat diet or of drugs to alter the cholesterol metabolism are being questioned by the experience that there is no good correlation of high cholesterol plasma levels with human atherosclerosis, and that the reduction of cholesterol intake has at times little or no effect on high cholesterol levels in man.[12] An important phase of arteriosclerotic vascular occlusion is the proliferation of the endothelial cells and fibroblasts and the presence of "embryonic cellular foci" with mitotic activity. Therefore, the use of drugs which inhibit cell division and others which delay connective tissue formation may be advantageous in the retardation of the arteriosclerotic process.

Summary

An attempt was made to elucidate the mechanism by which narrowing and occlusion of arteries occurs in arteriosclerotic softening of the brain. In an extensive histologic examination of 20 brains with arteriosclerotic encephalomalacia, no evidence of the occurrence of true thrombosis was observed.

As the microscopic study progressed, emphasis shifted from the lipid deposit to the fibroblastic part of the atherosclerotic plaque as the major factor in the obliterative sclerosis. The presence of "embryonic foci of cellular proliferation" in the plaque appear to be the source for the slow extension of the fibroblastic obliteration in the large cerebral and other vessels, such as the coronary arteries. In the small cerebral arteries, occlusion is caused by endothelial proliferation. The proliferative changes of the endothelial cells in the small cerebral vessels, as well as the proliferation of the fibroblasts in the atherosclerotic plaques, is viewed as a morbid process occurring at a time in the individual's life, when various cell types show great propensities for abnormal growth.

Summario in Interlingua

Esseva studiate le cerebros de 20 patientes con arteriosclerosis cerebral. Le objectivo del studio esseva le determination del exacte mechanismo de occlusion de arterias in encephalomalacia. Le datos histologic assi colligite ha convincite le autor que le concepto de "thrombosis cerebral" in su currente application general es erronee. Il occurre occlusion arterial, sed le mechanismos de su production non es illos usualmente acceptate. Le ver mechanismos es discutite.

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Normal Standards for Amplitude of Ballistocardiograms Calibrated by Force

By Isaac Starr, M.D.

Normal standards for ballistocardiogram amplitude have been estimated by statistical methods from a series of 194 healthy men and women. The application of new knowledge of the genesis of ballistocardiograms has resulted in normal standards with a smaller scatter than those previously formulated, and so the ability to detect cardiac abnormality has been correspondingly increased.

BALLISTOCARDIOGRAMS may indicate abnormality because they are too large or too small in amplitude; or because the contour of the record is abnormal. Determination of abnormality from the contour, a purely qualitative approach, has been the more popular method. The quantitative approach is more difficult, and to determine abnormality in amplitude, one must possess both normal standards and a ballistocardiograph which can be calibrated. But, obviously, a quantitative approach, if feasible, would permit finer distinctions and so would be more rewarding.

From the very first,[1] it seemed likely that the amplitude of the record had quantitative meaning, for whenever circumstances caused the subject's heart to beat more strongly, as after exercise, the record increased markedly in amplitude. More recently, the results of experiments[7] have demonstrated that the quantitative relationship between ballistocardiographic amplitude and certain aspects of cardiac force is closer than we had expected. This has encouraged us to seek once more to improve the normal standards in the light of the newer knowledge of the genesis of ballistocardiograms. These standards have been in need of improvement.

Our first normal standards for the amplitude of ballistocardiograms were published in 1941,[9] and they were related to attempts to measure cardiac output from these records. However, we soon became aware of theoretical objections to the formulae employed to estimate stroke volume in this early work, and when these were corrected by the omission of the factor for aortic size, the scatter of results secured in healthy persons increased considerably.

Later, Tanner,[2] using a method based on multiple regression equations containing items for body surface area and age, as well as measurements secured from the ballistocardiogram, provided normal standards for estimates of stroke volume from the ballistocardiogram having a smaller scatter, the deviations for men and women respectively being 13.4 per cent and 11.0 per cent of the mean values.

Somewhat later, normal standards for ballistocardiogram wave areas, pulse rate and body weight were made up without attempting to estimate stroke volume,[3] these studies yielded standard deviations which were about 16 per cent of the mean in persons under 40 years of age. Still later, after the results of the initial cadaver experiments had been analyzed, a variety of normal standards for "cardiac" force were set up,[4] using the sum of the vertical I + J distance of the largest and the smallest waves of the respiratory cycle. In these, the scatter was considerably larger, the standard deviation of the equation we most frequently used being 24 per cent of the mean value.

Direct measurement of the I and J wave altitudes has also shown a large scatter in data secured in healthy persons. In our data,[10]

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n adjustment was made for difference in body ize, men and women were studied together, nd the subjects were grouped by decades. Thus handled, the averages of the standard leviations of the I and J wave altitudes of ubjects from 20 to 49 years of age, expressed n per cent of the means of each decade, were similar, both being 28 per cent. In the results ecured in the large series of healthy persons, reported by Scarborough and his co-workers,[5] he data were treated somewhat differently; men and women were studied separately, and there was no adjustment for differences in body size; the standard deviation of the I wave of both sexes averaged 26 per cent, of the J wave 23 per cent, in persons from 20 to 50 years of age. In both these formulations, the I and J waves were measured separately; therefore, the scatter was increased by the error involved in placing the base line, which can be avoided by measuring directly from the I to the J wave tips, as has been done in the statistics to be reported in this paper.

Thus, for a considerable time the experience was discouraging, for it seemed that the scatter of results secured in healthy persons was proving to be so large that our ability to identify abnormality of the cardiac contraction from measurements of the waves was far less than we had hoped. Indeed, our early attempts to improve the normal standards in the light of increasing knowledge of the genesis of the ballistocardiogram, not only failed to accomplish this, but actually made matters worse by yielding normal standards with larger scatters. However, since these results were published, quantitative knowledge of the physiological genesis of ballistocardiograms has increased much further. The technique of simulating systole at necropsy, improved in many ways,[6] and gave much better quantitative information about the relation of the ballistic amplitude to the forces generating it,[6] information sure to be helpful in designing better normal standards. This and other evidence[2, 5, 7, 8] suggested that, to secure the best normal standards, there were three requirements: first, data from men and women should be considered separately; second, the square root of the measurements made on the ballistocardiogram should be used, rather than the measurements themselves; and third, factors related to the size of the subject should be omitted, even though we were seeking a measure of cardiac strength per unit of body size.

Thus guided, we have calculated new standards for amplitude of ballistocardiograms of healthy persons as a measure of cardiac force, and find that they are the greatest improvement over the previous formulations, for in some the scatter has been reduced until the standard deviation of the data in healthy young persons is only about 10 per cent of the mean value. So, by using these new standards, our ability to detect abnormality of the strength of the cardiac contractions should be greatly increased. In this presentation we introduce these new standards and give instructions for their use.

Material, Methods and Results

From the original normal series of ballistocardiograms[9] taken on healthy persons in 1937, 1938 and 1939, we have eliminated all records from persons who subsequently developed any serious disease, and there remained 56 young men and 48 young women from 20 to 39 years of age. This is a remarkably fine series because the normality of the cases at the time of the test has been established by the fact that they remained in good health for many years. This group will be called our selected series of healthy young adults, and there is a strong argument for basing our normal standards on these data alone. But as we proposed to analyze the data secured from men and women separately and to investigate the effect of age, the series seemed too small and too restricted in age range to be ideal for this purpose. So we added more data from the original series by including 42 healthy persons from 40 to 49 years of age, and also data from results secured from other healthy persons from 20 to 49 years of age, who had been tested after the original series had been completed. All these latter were tested over five years ago and none are known to have developed any serious disease up to the present time. The inclusion of these gives a total of 106 healthy men and 88 healthy women, which we will

speak of as the enlarged series. The failure to record measurements of wave duration and blood pressure in a few of the early tests has slightly diminished the number available for statistical analysis in some aspects of this study.

In order to aid in keeping track of these subjects in the succeeding years, the great majority had been secured from the more stable parts of the population of the hospital and medical school. So they consisted chiefly of doctors, medical students and their wives, of medical secretaries and technicians, and of the family and friends of the author. In a few instances, in the enlarged series, the same person has been used twice, when he or she had a second test 10 years or more after the first, and the data fell into a different age group.

The use of this group as a basis for normal standards for the whole population has certain disadvantages. Only the white race is represented, and it should be pointed out that the series does not include persons regularly engaged in hard physical labor.

Despite my large experience, it seemed wiser not to include data secured from medical students taking part in class experiments in which drugs were to be given them, as I feared that apprehension would warp the results.

All subjects were tested after lying at rest on the ballistocardiograph for a period of at least 15 minutes. Our original instrument was used;[1] it was of the resisted table type. No tests were made on any subject within two hours of completing a meal. Care was always taken that the subjects' heels were firmly pressed against the foot plate when the record was taken. So the standards to be described are those of resting persons, and no attempt was made to have the subjects in the strictly basal state.

Statistical analysis of the measurements made on the records secured on these subjects form the basis of the normal standards to be presented. These were performed by standard statistical methods with the aid of a Marchand calculator.

The type of normal standard finally adopted stemmed from the relations discovered in the data secured in the more recent cadaver experiments.[7] The regression giving the highest correlation discovered in a previous study,[7] i which the maximum velocity of the cardia ejection was used as our measure of cardia force is as follows:

$$\textit{Cardiac stroke force} = (\textit{body surface area})[51\sqrt{I+J}+5] \quad (1$$

where body surface area is in square meters an I + J is the vertical distance between the tip of I and J waves of the ballistocardiogram when a force of 280 Gm. displaces the ligh spot 1 cm., as is standard for our instruments The solution of this equation does not giv cardiac force in absolute units but simply a figure which one has good reason to believe is related to it; a conception based on evidence previously discussed.[7]

However, it seems obvious that to make normal standards we need a measure of cardiac strength in units related to the size of the subject, for obviously one has every right to expect that large persons will have stronger hearts than small ones, so, after dividing equation (1) by body surface area and, in order to compensate for the respiratory variations, using the average amplitudes of typical large and small waves of the ballistocardiogram for the single value used in equation (1) we have

$$\frac{\textit{Cardiac stroke force}}{\textit{Body surface area}} = 51\sqrt{\frac{I+J+I_2+J_2}{2}}+5 \quad (2)$$

where I and J and I_2 and J_2 are the vertical amplitudes of the waves of typical large and small complexes of the respiratory cycle of any record, expressed as in equation (1).

As cardiac stroke force is to be expressed only in relative units, we can ignore any coefficient the left side of this equation might obtain and slightly simplify the estimate by basing the standards on the sum of the amplitudes of the large and small waves rather than on their average, so we have

$$\frac{\textit{Cardiac stroke force}}{\textit{Body surface area}} = 51\sqrt{I+J+I_2+J_2}+7 \quad (3)$$

To further simplify formula (3), since the

TABLE 1.—*Normal Standards for Amplitude of Ballistocardiograms. Statistcs from Series of Healthy Young and Middle Aged Adults*

No.	Aspect Studied		Group Studied		Results		
	In general	Measurements Analyzed	No. and Sex	Age Range	Mean	Standard Deviation	
							in % of mean
1	Wave altitudes (select series)	$\sqrt{I + J + I_2 + J_2}$ *mm.*	56 M	20–39	5.4 *mm.*	0.58 *mm.*	10.7%
			48 F	20–39	4.4 *mm.*	0.49 *mm.*	11.2%
2	Wave altitudes × pulse rate	$\sqrt{I + J + I_2 + J_2}$ *mm.* × rate *per min.*	56 M	20–39	385.	52.5	13.7%
			48 F	20–39	318.	55.5	17.4%
3	Wave altitudes (enlarged series)	$\sqrt{I + J + I_2 + J_2}$ *mm.*	106 M	20–49	5.3 *mm.*	0.66 *mm.*	12.5%
			88 F	20–49	4.5 *mm.*	0.62 *mm.*	13.8%
4	Wave areas (enlarged series)	$\sqrt{I + J + I_2 + J_2}$ *mm. sec.*	103 M	20–49	0.83 *mm. sec.*	0.11 *mm. sec.*	13.3%
			81 F	20–49	0.67 *mm. sec.*	0.07 *mm. sec.*	10.4%
5	Wave areas × pulse rate	$\sqrt{I + J + I_2 + J_2}$ *mm. sec.* × rate *per min.*	101 M	20–49	81.	12.2	15.0%
			81 F	20–49	68.	12.4	18.3%
6	Values related to "work" per beat derived from wave areas	$\sqrt{I + J + I_2 + J_2}$ *mm. sec.* × mean B.P.	98 M	20–49	122.	16.0	14.1%
			81 F	20–49	89.	12.6	14.2%
7	Values related to "work" per min. derived from wave areas	$\sqrt{I + J + I_2 + J_2}$ *mm. sec.* × mean B.P. × P.R.	98 M	20–49	7952.	1351.	17.0%
			81 F	20–49	6408.	1384.	21.6%

regression so nearly passes through the origin, one can omit the added constant; and since our interest is confined to relations rather than absolute values for the left side, we can omit the slope also, obtaining:

$$\frac{\textit{Cardiac stroke force}}{\textit{Body surface area}} = \sqrt{I + J + I_2 + J_2} \qquad (4)$$

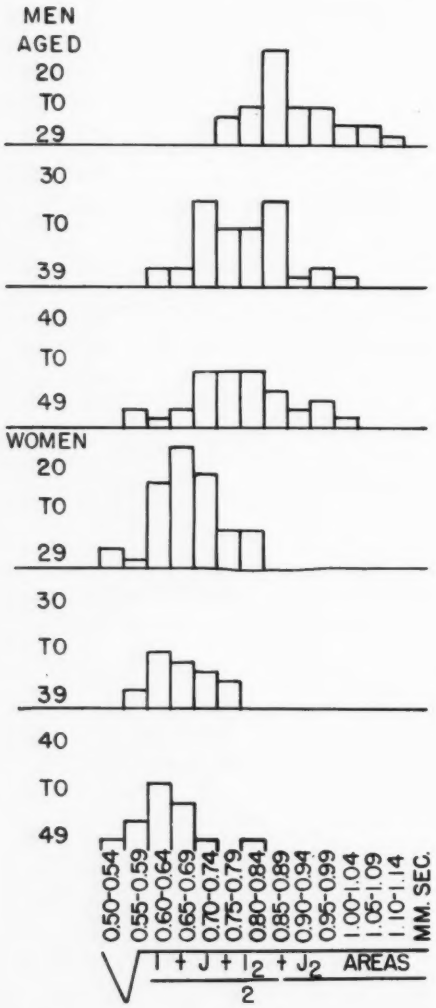

FIG. 1. Frequency diagram of the square root of average wave areas found in men and women in the first three decades of adult life. The smallest rectangle shown represents a single unit.

The units of measurement of the amplitude of the waves could be most readily expressed in millimeters by those using the standard calibration we employ (10 mm. = 280 Gm.) but knowing the relationship between amplitude and force one could also express the magnitude of the deflection in units of force such as grams or dynes.

No further simplification is possible, so we propose to employ equation (4) for the construction of normal standards, using the right side as our measure of cardiac stroke force related to body size. Accordingly, the square root of the sum of the vertical amplitudes of typical large and small waves was determined for each normal subject and the data subjected to statistical analysis. The results using both the selected and the enlarged series are given in table 1.

Several other types of normal standards were also explored. The regression equation relating the *area* of the I and J waves to cardiac stroke force in relative units has been previously published,[7] and it resembles equation (1) in character. Therefore for the same reasons as are given above it is proper to simplify it to:

$$\frac{\textit{Cardiac stroke force}}{\textit{Body surface area}} = \sqrt{I + J + I_2 + J_2 \textit{ areas}} \qquad (5)$$

where the waves are measured as triangles and their areas are expressed in millimeter seconds, or as dyne seconds. A frequency diagram of these results is presented as figure 1, and other statistics are in tables 1 and 2.

It also seemed desirable to explore the normal values when pulse rate was used as a factor by employing an equation which yielded an abstract value which might be called cardiac force per minute, as follows:

$$\frac{\textit{Cardiac force per minute}}{\textit{Body surface area}} = \sqrt{I + J + I_2 + J_2} \times \textit{pulse rate} \qquad (6)$$

This was estimated from wave amplitudes of the 104 healthy young persons of the selected series with the results shown in table 1, no. 5, and pulse rate was similarly employed in the

TABLE 2.—*Normal Standards for Amplitude of Ballistocardiograms. Regression Equations Allowing for the Effect of Age on Ballistocardiograms*

No.	Aspect Studied	Regression Equation	Group Studied		Standard Deviation About the Regression	
			No. & Sex	Age Range		
						As % of Mean
8	Wave altitudes	$\sqrt{I + J + I_2 + J_2}$ *mm.* = −0.04 Age *years* + 6.68	105 M	20–49	0.60 *mm.*	11.3%
		$\sqrt{I + J + I_2 + J_2}$ *mm.* = −0.03 Age *years* + 5.45	87 F	20–49	0.53 *mm.*	11.8%
9	Wave areas	$\sqrt{I + J + I_2 + J_2}$ *mm. sec.* = −0.0071 Age *years* + 1.4	101 M	20–49	0.142 *mm. sec.*	12.1%
		$\sqrt{I + J + I_2 + J_2}$ *mm. sec.* = −0.0042 Age *years* + 1.07	81 F	20–49	0.085 *mm. sec.*	9.0%
10	Wave areas × pulse rate	$\sqrt{I + J + I_2 + J_2}$ *mm. sec.* × pulse rate *per min.* = −0.608 Age *years* + 102.3	101 M	20–49	11.0	13.6%
		$\sqrt{I + J + I_2 + J_2}$ *mm. sec.* × pulse rate *per min.* = −0.495 Age *years* +82.4	81 F	20–49	11.6	17.0%

construction of the regression equation in table 2, no. 10.

In the normal standards given in table 1, the age of the subjects was neglected, although the diminution in average size of ballistocardiograms as age advances is well known,[5, 10] a diminution which may take place even though good health commensurate with one's age is maintained. Therefore, regression equations defining the relation of the age of the subjects to both the amplitudes and the areas of the I and J waves were calculated, and the results are given in table 2. The use of these regressions accomplishes a small reduction in the scatter and these equations may also be used as normal standards.

As it is obvious that the resistance against which the heart expells its blood must be considered in any estimate of its strength, we also explored the effect of multiplying the square root of the wave areas by the mean blood pressure defined as the sum of the systolic and diastolic pressures divided by 2. The correlation of these products with the ages of the subjects was not significant, the regression being almost horizontal, so the increase of blood pressure as age advances neutralizes in large measure the effect of the diminution of the ballistocardiogram amplitude, which also takes place as one grows older. Therefore we have not demonstrated that age is a significant factor in what is a kind of cardiac work, and the regression equation has been omitted from table 2 for this reason. The means of the values obtained in the enlarged series and the scatter around them are given in table 1, no. 6

The products of the square root of wave areas, mean blood pressure and pulse rate, represent a type of cardiac work per minute. The means and the standard deviations about the means have also been given in table 1, no. 7.

Discussion

The reason for the wide scatter of our previous formulations of data[3, 4, 10] secured on healthy persons is now obvious. The measurements of the I and J waves[5, 10] scatter widely because the data is skewed, and points outlying far on the high side greatly increase the standard deviation. Using the square root of the measurements abolishes this skewness and greatly reduces the scatter. In other formulations, although the square root was employed—our original theoretical conceptions[1] had indicated that the square root should be used—the data secured in men and women were combined and some aspect of body size such as actual or ideal weight, or body surface area, was relied upon to compensate for differences between the sexes. This has proved to be a poor plan be-

cause it appears that women's hearts are weaker than men's hearts, not because women are smaller but for some more subtle reason. On second thought, this does not seem unexpected; doubtless, an athletic contest conducted between men and women of similar weight would prove the men to be the stronger. When the sexes are treated separately the scatter of the normal standards is much improved.

The thought that body size should play no part in constructing normal standards came to us as a surprise. It does, of course, play a part in our theoretical conceptions, for *force* = *mass* × *acceleration*, but, when an estimate of cardiac strength in terms of body size is sought, the effect of body size cancels out. The lack of this knowledge was an important factor in the large scatter of the older standards.

One now sees the reason for the small scatter in our first formulation.[9] The use of the factor "A", an estimate of aortic cross-section area derived in part from body size, supplied the need for a factor related to body size in the numerator of the equation; we did the right thing for the wrong reason, and when "A" was omitted from the estimate, the scatter increased markedly. Tanner's formulation[2] conforms most closely to the present conceptions and the scatter of these results was but little larger than that of the best of our present formulations.

Comparison of the scatter of the square root of the wave areas (table 1, no. 4) with that of wave altitudes (table 1, no. 3) indicates that the former formulation is superior. In males the difference in scatter is not significant, but in females the wave areas are significantly less scattered. There are many reasons for thinking that wave areas would provide more useful normal standards for clinical work than would wave altitudes. Different pressures of the subject's heels against the foot board,[11] or the error of forgetting to have the subject's heels in contact with the foot board, may cause a measurable difference in wave altitudes, but as wave duration increases as height decreases, such differences of technique cause less, if any, differences in I and J wave areas. Similarly, differences in the weight of tables, judging from the effect when iron bars are added to our light tables,[9] affect wave areas less than they do wave altitudes. Also, fine vibrations superimposed on the ballistocardiogram, such as is caused in our records by vibrations in the building, may markedly distort the height of wave tips, but they have much less influence on wave areas. Finally in cadaver experiments in which asynchronous systoles of the two sides of the heart were simulated, the height of the resulting distorted waves was far more affected than the areas. In short there are many reasons to prefer wave areas to wave altitudes for quantitative work in the clinic although in our series the gain is not great.

Studying the regression equations for square root of wave altitudes in terms of age (table 2, no. 8) one finds that the amplitude of the ballistocardiograms of men diminishes more rapidly than that of women as age advances; this is true of the data of Scarborough and his associates[5] also. And, as one would expect, the scatter about the regression is smaller than when age is not considered. This is especially true of the data secured on women. The data concerned with wave areas behaves similarly and the scatter about the regression of the square root of wave areas on age is the smallest we have encountered, the average of the standard deviations of men and women being 10.5 per cent of the mean values, which seems as good or better than that of most clinical methods now in use. Figure 1 gives a frequency diagram of the wave areas in different age groups, and the tendency for the results to conform to a bell-shaped curve in each of the age groups is most encouraging. This is the most satisfactory formulation that we have found, and it should be easy to identify abnormal cardiac performance by means of it.

When the square root of the amplitude of ballistocardiograms is multiplied by the pulse rate, to get a measurement related to cardiac strength per minute, the scatter of our normal standards increases significantly. The consistency of the data secured on women was disturbed by the results secured on several who, perhaps excited by the test, had unusually high pulse rates during it; but we have not omitted these results from the statistical analysis. Despite the large scatter, the use of equa-

tions given in table 2, no. 7, might well permit one to detect an important type of clinical abnormality which would be missed if attention were focused exclusively on measurements of cardiac function per beat.

The use of the product of some aspect of the ballistocardiogram amplitude and the mean blood pressure has much to commend it, and equations providing normal standards for such values are given in table 1, no. 6 and 7. Certainly any estimate of the strength of the heart would benefit by taking into account the resistance against which the blood is ejected. But, while it is easy to multiply ballistic measurements by mean blood pressure and to estimate empirical normal standards for the product, the difficulty of making a satisfactory physiological interpretation of the result is formidable.

In our cadaver experiments injections into the aorta and the pulmonary artery could be made separately, and the relation of the two effects explored.[4] In the best experiment, the aortic ballistocardiogram was much larger, the I + J distance being twice, and the I + J wave areas almost four times the size of the corresponding deflections which followed the injection into the pulmonary artery; and the two injections were judged to be similar not only because the total amount injected was similar, but also because the contour of both injection curves was very similar. Evidently, the ballistic effect produced by the right side of the heart, while much smaller than that of the left, is far from negligible.

During life the contribution of the right ventricle to the ballistocardiogram has been judged to be considerable, because in healthy persons, that record begins to increase in amplitude at the onset of inspiration, and so at the time when the diminishing pressure in the chest would cause better filling of the right heart, and before better filling of the left heart would be expected.[19]

In the clinic we can readily measure only the pressure which opposes the expulsion of blood from the left ventricle; but the major part of the heart's work is performed by this ventricle, and it also produces the larger part of the ballistocardiogram, so one can properly hope to secure a rough approximation of the relative magnitude of cardiac work in different subjects by multiplying the amplitude of the ballistocardiogram by the peripheral blood pressure, even though the contributions of the right side of the heart are unknown.

Another theoretical difficulty must be pointed out; the product of ballistocardiogram amplitude and mean blood pressure does not give an estimate of work in the Newtonian sense, for cardiac work of this kind is estimated from the product of cardiac output and pressure, while the ballistocardiogram wave altitudes and areas are not closely related to cardiac output unless a time factor is introduced into the calculation. It is proper to think of the amplitude of the systolic ballistic waves as related to acceleration,[7] and the product of pressure and acceleration represents something different from Newtonian work as defined by physicists. But work as defined by the physicists is something different from what doctors have in mind when they use the word "work"; for example, according to the Newtonian conceptions, the giant Atlas, while supporting the world on his shoulders, does no work at all, a statement which would seem ridiculous to any doctor concerned with Atlas' health. So perhaps work of the Newtonian kind is not what doctors should seek when we wish to measure cardiac performance.

Because the square roots of the altitudes and areas of the ballistic I and J waves are related to acceleration, one has the right to think that the product of such values and the mean blood pressure would be related to the tension time of the heart muscle, to use a term introduced by Hartree and Hill.[12] Tension time was employed by these authors as a measure of the performance of skeletal muscles, and I have made use of a somewhat similar idea,[13] the product of mass and acceleration with respect to an object falling in the gravitational field, to estimate muscular work performed in supporting, lifting and lowering heights, in weight-lifting experiments. I believe that a conception of muscular performance such as this may well meet the doctors' needs more readily than the classic Newtonian conception of work; by my equations, Atlas is found to be doing very

heavy work when supporting the world. In any event, though certainly not identical with Newtonian work, the products of the square root of the I and J wave altitudes and mean blood pressure have been found to be strongly correlated with Newtonian work in our cadaver experiments,[16] so I have not hesitated to place the normal standards for these values in table 1.

Thus the general character of satisfactory normal standards for amplitude of ballistocardiograms now seems clear and the small scatter of our best formulations has reassured us about several features of our procedure.

It has long been known that the deviation of duplicate ballistocardiograms taken by our apparatus and technic, in individuals on the same day, and on different days, was small;[2, 9, 14] and the results contained in this presentation demonstrate that there is also a satisfactory stability of the physiological function we are measuring from person to person. Also, since the male subjects studied ranged from 280 pounds to 125 pounds in weight, and from 74 to 61 inches in height; and the females from 183 pounds to 97 pounds in weight, and from 71 to 52 inches in height, it seems evident that differences in body size and configuration play no important role in the amplitude of ballistocardiograms secured by our apparatus and technique, a conclusion in accord with Tanner's results.[2] It also seems evident that inevitable small differences in technique, such as different pressures of the heels against the footplate, also cause no noteworthy differences of result. In short, the ability to get such stable values in a large and diverse series of healthy persons has greatly increased our confidence in the ability of our method to detect abnormality due to disease.

Consideration of the results of the statistical analysis summarized in tables 1 and 2 has enabled us to design a simple procedure for the routine detection of abnormality of amplitude of ballistocardiograms, which has proven both useful and easy to apply. From the results recorded in table 1, no. 1, I have constructed table 3, which permits one to determine the normality of the amplitude of the ballistocardiogram of any subject, in terms of that of the healthy young adults of the selected series, without a calculation. To apply the method, one should proceed as follows:

With the whole ballistocardiogram before one, one selects by inspection a typical large and a typical small complex of the respiratory cycle, and measures the vertical distance between the tips of the I and J waves of each complex. If the ballistocardiogram is calibrated as my instruments are, 10 mm. of deflection representing 280 Gm. of force, the sum of the two vertical IJ distances is found in column 1 or 4 of table 3, and the normality of

TABLE 3.—*This Permits Ready Detection of the Abnormality of the Amplitude of any Record, by Comparison with that of Healthy Young Adults*

Sum of Amplitudes of Typical Large and Small Complexes ($I + J + I_2 + J_2$)		Relation to Means of Healthy Young Adults		Sum of Amplitudes of Typical Large and Small Complexes ($I + J + I_2 + J_2$)		Relation to Means of Healthy Young Adults	
		Males	Females			Males	Females
mm. (std. calibration)	*Force, gms.*	%	%	*mm. (std. calibration)*	*Force, gms.*	%	%
60	1680	+43	+77	30	840	+1	+25
59	1652	+42	+76	29	813	−1	+23
58	1625	+40	+74	28	785	−3	+21
57	1596	+39	+73	27	756	−4	+19
56	1569	+38	+71	26	728	−6	+17
55	1540	+37	+70	25	700	−8	+14
54	1514	+35	+68	24	672	−10	+12
53	1485	+34	+67	23	644	−12	+10
52	1456	+33	+65	22	616	−14	+7
51	1429	+32	+63	21	588	−16	+5
50	1400	+30	+62	20	560	−18	+2
49	1372	+29	+60	19	532	−20	0
48	1355	+28	+59	18	504	−22	−3
47	1317	+26	+57	17	476	−24	−6
46	1289	+25	+55	16	448	−26	−8
45	1261	+24	+53	15	420	−29	−11
44	1232	+22	+52	14	392	−31	−14
43	1205	+21	+50	13	364	−34	−18
42	1176	+19	+48	12	336	−36	−21
41	1149	+18	+46	11	308	−39	−24
40	1121	+17	+45	10	280	−42	−28
39	1092	+15	+43	9	252	−45	−31
38	1065	+14	+41	8	224	−48	−35
37	1036	+12	+39	7	196	−51	−39
36	1009	+11	+37	6	168	−55	−44
35	981	+9	+36	5	140	−59	−49
34	953	+7	+33	4	112	−63	−54
33	924	+6	+31	3	84	−68	−60
32	896	+4	+29	2	56	−74	−68
31	858	+3	+27	1	28	−82	−77

Normal limits mean $\pm 2\sigma$ = +21% to −21% for males.

Normal limits mean $\pm 2\sigma$ = +22% to −22% for females.

the result in terms of the deviation from the expected value is found by moving over to the column marked "Men" or "Women," depending on the sex of the subject. The calculation involved in making the table dispenses with the necessity of taking the square root when it is used.

For example, if the sum of $I + J + I_2 + J_2$ *altitudes* = 32 mm., and the subject is male, we find that this result is 4 per cent above the expected value. If $I + J + I_2 + J_2$ *altitudes* = 15 mm., and the subject is a woman, the answer is −11 per cent. If one chooses to use 2σ as normal limits, these are, for males, ±21 per cent; for females, ±22 per cent.

If the ballistocardiogram is not calibrated as are my own instruments, one can enter table 3 by the force equivalent to the sum of the deflections of the large and small waves, by using the second and fifth columns of table 3; and obtain the same result for instruments which are standardized against force.

The use of this table suffices to determine the normality or abnormality of the amplitude of the great majority of records with sufficient accuracy for most clinical work but, if one wishes to obtain further information, or to discover whether an abnormality indicated by the use of table 3 can be accounted for by the patient's age, one can use the equations of table 2, no. 9, to give an expected value, to which the area of the I and J waves found in the patient's record can be compared.

For example: if one finds that in a male, age 53, a typical large complex has an I wave altitude of 5 mm., a duration of 0.08 second, and a J wave altitude of 10 mm., and a duration of 0.10 second; and that in the typical small complex, I_2 = 4 mm. and 0.06 second, J_2 = 8 mm. and 0.08 second, then:

$$\text{Area } I = \tfrac{1}{2}(5 \times 0.08) = 0.20 \text{ mm. second}$$
$$\text{Area } J = \tfrac{1}{2}(10 \times 0.10) = 0.50 \text{ mm. second}$$
$$\text{Area } I_2 = \tfrac{1}{2}(4 \times 0.06) = 0.12 \text{ mm. second}$$
$$\text{Area } J_2 = \tfrac{1}{2}(8 \times 0.08) = 0.32 \text{ mm. second}$$

and $I + J + I_2 + J_2 = 1.14$ mm. sec. and $\sqrt{I + J + I_2 + J_2} = 1.07$. The expected $\sqrt{I + J + I_2 + J_2}$ is estimated by inserting the age in the equation for males found in table 2, no. 9. Thus

$$\text{Expected } I + J + I_2 + J_2$$
$$0.0071(53) + 1.4 = 1.02$$

The difference between found and expected values = 1.07 − 1.02 = 0.05.

Since the standard deviation about the regression is 0.142, $t = \frac{0.05}{0.142} = 0.35$. This value being less than 2, the difference is not significant, and the result is within normal limits. If t exceeds 2, the chances of abnormality exceed 20 to 1, and this defines the conventional limits of normality.

The other regression equations in table 2 could be used similarly, if one felt the need of information of the kind they supply.

I hope that I have not confused readers by using the sum of measurements of large and small complexes, rather than their average, in constructing these normal standards. This was done simply to save the step of averaging. Needless to say, the average is of greater theoretical interest, but the use of the sum suffices equally well to distinguish normal from abnormal amplitudes.

Finally one must ask oneself the question: To how many of the different types of ballistocardiograms now in use, would these standards be applicable? I fully expect that the general form of the equations which have so diminished the scatter of our results, defines important physiological relations, the knowledge of which will prove useful in designing normal standards for results secured by any of these instruments. I am also hopeful that the standards themselves will be found useful for assessing results secured by instruments that can be standardized against force, which includes not only resisted tables calibrated by a suspended mass, the type I employ, but also nonresisted tables whose acceleration is recorded and which are calibrated by means of the acceleration of a pendulum.[15] In theory, these two types should give similar records. At the moment, it is hard to say whether these standards will prove to be applicable to results secured by the Dock method[18] or not, but I am hopeful that they may, when the means of calibrating these instruments have been improved. But these standards could not be applied to results secured by tables of the Nickerson type,[17] without a major revision.

Nevertheless, as factors such as weight of the table make a difference in the amplitude of records taken by resisted tables, and as there may well be other disturbing factors not yet clearly identified, it seems wise to recommend that all workers in the field confirm the applicability of my data to their results by comparing my averages with those secured in

normal subjects by their own instruments. For example, the mean values of the I and J wave altitudes of healthy men and women between 20 and 49 years of age in the ample data of Scarborough and his coworkers[5] indicate a $\sqrt{I + J + I_2 + J_2}$ about 15 per cent higher than the values we obtained, a difference probably to be attributed to the heavier table used by these authors, as adding weight to my own table increases the amplitude of my records. It should be easy to adjust the normal standards given in this paper to compensate for differences such as this.

Summary

To obtain new and improved normal standards for the amplitude of ballistocardiograms, as a measure of force of the cardiac beat, we have restudied results secured in a series of 146 healthy persons tested over 15 years ago. The great majority of these subjects have been carefully followed ever since and those who subsequently developed cardiovascular disease have been eliminated. To secure greater numbers for certain aspects of the analysis, 48 healthy persons, tested at later dates, have been added, but to allow time for the development of unrecognized cardiac disease in the added group, no results secured in tests made within the last five years have been included.

Normal standards have been defined by statistical analysis of these results. These standards can only be applied to ballistocardiograms from instruments which can properly be calibrated in terms of force. The absolute values for cardiac force or for the other aspects of cardiac function measured by the ballistocardiogram cannot be given at this time but the relation of results secured on any subject to the normal can be readily determined.

New knowledge of the genesis of the ballistocardiogram has resulted in marked improvement over our previous normal standards, for in the results here described the scatter about the mean is smaller, the standard deviation about the mean being close to 10 per cent of the mean value in the most promising formulations.

For use as a screening test, a table is given in which the normality of the I and J wav altitudes, in terms of results secured on health young adults, can be read off without a com putation.

Regression equations defining the effects c age on the normal values are also given, th amplitude of the record diminishes as age ad vances, as is well known, and these equation can be used to determine the normality o abnormality of the values secured in an patient.

When measurements of the square root o the amplitude of ballistocardiograms ar multiplied by the pulse rate, a product i secured which might well have clinical valu Normal standards for this product are given, but the scatter of the results secured exceeds that when the amplitudes alone are used.

When measurements related to the square root of the amplitude of ballistocardiograms are multiplied by the mean blood pressure, the correlation of the product with age is no longer significant for either men or women between 20 and 50 years of age. The relation of this product to the work of the heart is discussed, and formulae defining the normal values are given.

Summario in Interlingua

Pro obtener nove e meliorate standards pro le amplitude ballistocardiographic interpretate como mesura del fortia del pulso cardiac, nos ha re-examinate le resultatos obtenite in un serie de 146 subjectos in bon stato de sanitate plus que 15 annos retro. Le grande majoritate de iste subjectos continuava ab ille tempore sub caute surveliantia, e omne illes qui subsequentemente disveloppava morbo cardiovascular esseva eliminate. Pro disponer de plus satisfacente numeros de casos pro certe aspectos de nostre analyse, nos ha includite in illo 48 personas in bon stato de sanitate qui esseva subjicite a examines ballistocardiographic a un tempore plus recente. Sed a fin de permitter un sufficiente lapso de tempore pro le disveloppamento de non-recognoscite morbo cardiac, nulle resultatos obtenite in examines durante le passate cinque annos esseva includite in le gruppo additional.

Standards normal esseva definite per

analyse statistic de iste resultatos. Le standards assi obtenite es valide solo pro ballistocardiogrammas facite con instrumentos que permitte un adequate calibration de fortia cardiac. Valores absolute de fortia cardiac e de altere aspectos del functionamento cardiac mesurate per le ballistocardiographo non pote esser determinate con nostre presente technicas; sed le resultatos obtenite in un date subjecto es prompte—e facilemente exprimibile in relation al norma.

Nostre meliorate comprension del genese del ballistocardiogramma ha resultate in un marcate melioration de nostre previe standards normal. In le resultatos hic describite le dispersion circa le valor median es plus parve que in previe studios: le deviation standard ab le valores median es vicin a 10 procento del valor median in le plus promittente formulationes.

Pro facilitar le classification preliminari de ballistocardiogrammas nos ha summarisate le resultatos obtenite ab juvene adultos in bon stato de sanitate a in un tabula per medio del qual le normalitate del altitude del undas I e J es verificabile sin computation.

Nos etiam presenta equationes de regression le quales defini le effectos del etate del subjecto super le valores normal. Il es ben cognoscite que le amplitude del registration regrede quando le etate del subjecto se avantia, e nostre equationes de regression pote esser usate pro determinar le normalitate o anormalitate del valores obtenite ab ulle patiente.

Quando mesurationes del radice quadrate del amplitude de ballistocardiogrammas es multiplicate per le rapiditate del pulso, le producto resultante es possibilemente de valor clinic. Nos presenta standards normal pro iste producto, sed le dispersion del resultatos obtenite excede le dispersion del amplitudes simple.

Quando mesurationes del radice quadrate del amplitude de ballistocardiogrammas es multiplicate per le valores median del pression sanguinee, le correlation del producto con le etate del subjectos cessa esser significative pro hominos e feminas inter 20 e 50 annos de etate. Es discutite le relation de iste producto al labor del corde. Nos presenta formulas que defini lor valores normal.

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The Electrocardiographic Pattern of Right Ventricular Hypertrophy in Chronic Cor Pulmonale

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The electrocardiographic patterns encountered in 28 patients with pulmonary hypertension secondary to chronic lung disease have been studied. Thirteen had neither right ventricular hypertrophy nor right bundle-branch block; eight had either right ventricular hypertrophy alone or right ventricular hypertrophy and right bundle-branch block (complete or incomplete); and seven had incomplete right bundle-branch block. A statistical comparison is made between these various groups of the means of the following physiologic measurements: mean pulmonary artery pressure, total pulmonary resistance, arterial oxygen saturation, right ventricular work, arterial carbon dioxide content, and cardiac index. The significance of the pattern of right ventricular hypertrophy is discussed.

JOHNSON AND ASSOCIATES[1] found in their study of patients with cor pulmonale secondary to chronic pulmonary disease that if the electrocardiographic pattern of right ventricular hypertrophy was present the mean pulmonary artery pressure usually exceeded 30 mm. Hg. Dexter and co-workers[2] have pointed out in their study of cases of cor pulmonale without hypoxia that the pattern of right ventricular hypertrophy did not appear until the total pulmonary resistance exceeded 750 dynes seconds cm.$^{-5}$

We have had the opportunity to study by cardiac catheterization 28 patients with pulmonary hypertension secondary to chronic lung disease. It was thought that a comparison of our results with those of Johnson and co-workers[1] and of Dexter and associates[2] would be of interest.

Material and Methods

The patients studied were from the medical service of the Cincinnati General Hospital and from the Veterans Administration Hospital, Dayton, Ohio. Some of these patients were included in a previous report from this laboratory.[3] All had the diagnosis of chronic lung disease established from history and/or chest x-ray study (tables 1 and 2).

Cardiac venous catheterization was carried out according to the method of Cournand and Ranges.[4] Cardiac outputs were determined by the direct Fick principle. Pulmonary "capillary" pressures were measured according to the method of Hellems, Haynes and Dexter.[5] Pressures were recorded by means of a five channel optical oscillograph (Hathaway). The zero point for pressures was 10 cm. anterior to the back of the patient when supine. The mean pulmonary artery and pulmonary "capillary" pressures were measured by planimetric integration.

Pulmonary arteriolar resistance[6] was calculated according to the formula:

$$R = \frac{PA_m - \text{“}PC\text{”}_m}{CO} \times 1332 \text{ dynes seconds cm.}^{-5}$$

Total pulmonary resistance[6] was calculated as follows:

$$R' = \frac{PA_m - O}{CO} \times 1332 \text{ dynes seconds cm.}^{-5}$$

Where PA_m = pulmonary arterial mean pressure in millimeters Hg; *"PC"* = pulmonary "capillary" mean pressure in millimeters Hg; CO = cardiac output, cubic centimeters per second; 1332 = conversion factor from millimeters Hg to dynes per square centimeter.

Right ventricular work[6] was calculated as follows:

$$W_r = \frac{(CI_r \times 1.055)([PA_m - RA_m] \times 13.6)}{1000}$$

·Kg.M./min./sq.M.

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TABLE 1.—*Physiologic Measurements in Thirteen Patients with Chronic Cor Pulmonale without Right Ventricular Hypertrophy or Right Bundle-Branch Block (Complete or Incomplete)*

Patient	X-ray	Pressures (mm. Hg)				Resistances (Dynes sec. cm.$^{-5}$)		Art. O_2 Sat. (% of Capacity) 94–100	Art. CO_2 Content (Vols %) 45–54	RV Work (Kg. *M.*/min./M.^{2}) 1.2	Cardiac Index (L./min/M.^{2}) 3.1± 0.4	Electrocardiogram					REMARKS
		RA −2 to +5	PC 5–13	PA S/D 11–29 / 4–13	PA Mean 8–19	PAR 47–160	TPR 125–250					Rhythm	Abnor. P WAVES	RVH	IRBBB	CRBBB	
J.Be. 63, W.M.	Pneumonia at apex LLL with abscess cavity	—	13	33/18	23	188	434	94.4	47.6	—	2.7	S	0	0	0	0	Asthma for 15 years. Autopsy: Bronchogen. carc., LLL. Emphysema. RV 3 mm. LV 11 mm.
G.Al. 59, W.M.	Congenital diaphragmatic hernia. Cardiac silhouette not well seen	12	12	60/30	41	478	676	75.5	61.6	1.18	2.9	S	0	0	0	0	VC 32%; MBC 28%. Spirogram: No emphysema. Polycythemia
M.L. 53, W.F.	Marked emphysema	1	6	33/13	21	337	471	89.3	—	0.70	2.4	S	+	0	0	0	No polycythemia
H.J. 58, W.M.	Emphysema, severe	3	—	8–34 / −10+20	17	—	232	86.5	—	0.85	4.2	S	0	0	0	0	Marked respiratory fluctuation of all pressures. Autopsy: Typical of asthma and emphysema. RV 7 mm. LV 18 mm.
E.J. 61, W.M.	Chron. bronch. infection and fibrosis, possibly with bronchiectasis. Emphysematous blebs	8	—	24–40* / 2–11	28†	—	625‡	89.1	59.7	0.56	1.9	S	+	0	0	0	Nodal rhythm on one occasion
A.B. 46, C.M.	—	4	12	36/14	22	103	226	95.1	—	1.02	3.9	S	+	0	0	0	Systemic press. 170/130. Mild emphysema clinically.
J.Sm. 52, W.M.	Marked emphysema	4	8	30/15	23	286	439	93.4	48.1	0.62	2.3	S	0	0	0	0	VC 80%; MBC 55%. Spirogram typical of pulmonary emphysema
L.N. 52, W.M.	Chron. lung disease with emphysema. Cor pulmon.	5	—	39/21	29.6	—	365	83.3	66.9	1.37	3.8	S	+	0	0	0	Polycythemia. Hemat. 52 → 62; VC 54%; MBC 27%
J.W. 38, C.M.	Chron. lung disease with emphysema. Prominent pulmonary artery	2	18	36/22	26	119	386	66.2	64.9	0.98	2.9	S	0	0	0	0	Polycythemia. Hemat. 54; VC 45%; MBC 29%. Autopsy: Diffuse emphysema. Cor pulmon. RV 10 mm. LV 15 mm.
M.S. 53, W.F.	Chron. lung disease with fibrosis and emphysema. Card. enlarge.	10	8	30/17	24	330	494	88.1	48.5	0.51	2.6	S	+	0	0	0	VC 106%; MBC 88%

For normal values, see References [2, 6, 27, 28, 30].

TABLE 1.—*Continued*

Patient	X-ray	Pressures (mm. Hg)				Resistances (Dynes sec. cm.$^{-5}$)		Art. O_2 Sat. (% of Capacity) 94–100	Art. CO_2 Content (Vols. %) 45–54	RV Work (Kg. M./min/M.^{2}) 1.2	Cardiac Index (L./min/M.^{2}) 3.1± 0.4	Electrocardigram					REMARKS
		RA −2 to +5	PC 5–13	PA S/D 11–29 / 4–13	PA Mean 8–19	PAR 47–160	TPR 125–250					Rhythm	Abnor. P WAVES	RVH	IRBBB	CRBBB	
H.Ir. 62, W.M.	Mild general. card. enlarge. (Bronch. asthma)	—	3	38/24	27	462	520	93.9	52.1	—	2.2	AF	—	0	0	0	VC 73%; MBC 27%
J.Fist. 55, C.M.	Emphysema and fibrosis. Large pulmon. art. compatible with cor pulmon.	4	12	55/20	32	293	454	78.1	60.8	1.28	3.2	S	0	0	0	0	ECG 1 yr. after catheter. showed RVH. Died 2 yrs. after catheter. No autopsy.
H.St. 51, C.M.	Emphysema. Pulmon. arc enlarged. Minimal RV enlarge. Cor pulmon.	3	7	72/18	33	400	507	85.6	56.3	1.40	3.2	S	0	0	0	0	ECG 2 yrs. after catheter. showed RVH.

For normal valves, see References[2, 6, 27, 28, 33].

RA: right atrium; PC: "pulmonary capillary"; PA: pulmonary artery; PAR: pulmonary arteriolar resistance; TPR: total pulmonary resistance; RV: right ventricular (or ventricle); RVH: right ventricular hypertrophy; IRBBB: incomplete right bundle-branch block; CRBBB: complete right bundle-branch block; VC: vital capacity, per cent of predicted; MBC: maximum breathing capacity, per cent of predicted.

* Right ventricular pressure.

† Right ventricular mean systolic ejection pressure.

‡ Total pulmonary resistance calculated using right ventricular mean systolic ejection pressure instead of mean pulmonary artery pressure.

Where W_r = work of right ventricle against pressure; CI = cardiac index, liters per minute per square meter; 1.055 = specific gravity of blood; PA_m = pulmonary arterial mean pressure, millimeters Hg; RA_m = right atrial mean pressure, millimeters Hg; 13.6 = specific gravity of mercury.

In three cases (R. P., E. J., R. W.) where no mean pulmonary artery pressures were available, the right ventricular mean systolic ejection pressure[6, 7a, 7b] was substituted in the above equations.

All patients had electrocardiograms consisting of the three standard leads, aV_R, aV_L, aV_F, V_1 through V_6 (and V_{3R} and V_{4R} in some), usually taken either on the same day or within a few days of the time of catheterization.

The criteria used for right ventricular hypertrophy[1, 8–10] were those of a qR pattern in V_{3R} or V_1, an R wave in V_1 of 7 mm. or greater, an R to S ratio in V_1 greater than 1, or a delay in the onset of the intrinsicoid deflection in V_1 of from 0.035 to 0.05 second. Incomplete right bundle-branch block[1, 11] was diagnosed on the basis of an rSR′ pattern in V_{3R} or V_1 with delay in the onset of the intrinsicoid deflection of R′ from between 0.05 and 0.075 second. If the height of R′ exceeded 10 mm. it was taken as evidence of right ventricular hypertrophy in addition to incomplete right bundle-branch block.[11] Complete right bundle-branch block[8, 12, 13] was diagnosed on the basis of a prolongation of the QRS interval in the standard leads to 0.12 second or greater with an rSR′ pattern in V_{3R} or V_1 and a delay in the onset of the intrinsicoid deflection of R′ to 0.08 second or greater. If the height of R′ exceeded 15 mm. it was taken as evidence of right ventricular hypertrophy in addition to complete right bundle-branch block.[13] The P waves in the standard leads were considered to be abnormal if they were 0.12 second or greater in duration or 3 mm. or more in height, or were notched.[14] Heart position was classified according to the criteria of Wilson.[8]

RESULTS

Part I

Our cases were divided into four groups: Group I, those without right ventricular hypertrophy or right bundle-branch block, complete or incomplete (13 cases); group II, those with right ventricular hypertrophy and/or right bundle-branch block, complete or incomplete (15 cases); group III, those with right ventricular hypertrophy alone or with both right ventricular hypertrophy and

TABLE 2.—*Physiologic Measurements in Fifteen Patients with Chronic Cor Pulmonale with Right Ventricular Hypertrophy and/or Right Bundle-Branch Block (Complete or Incomplete)*

Patient	X-ray	Pressures (mm. Hg)				Resistances (Dynes sec. cm.$^{-5}$)		Art. O_2 Sat. (% of Capacity) 94–100	Art. CO_2 Content (Vol. %) 45–54	RV Work (Kg. M./min./M.^{2}) 1.2	Cardiac Index (L./min./M.^{2}) 3.1±0.4	Electrocardiogram					REMARKS
		RA −2 to +5	PC 5–13	PA S/D 11–29 / 4–13	PA Mean 8–19	PAR 47–160	TPR 125–250					Rhythm	Abn. P WAVES	RVH	IRBBB	CRBBB	
C. B. 57 W.M.	Emphysema. Large right vent. Cor pulmon.	17	—	90/45	59	—	1469	51.3	65.7	1.26	2.1	S	+	+	0	0	Polycythemia
M. T. 45 W.M.	Emphysema and fibrosis. Large pulmon. art. compatible with cor pulmon.	10	—	45/27	37	—	744	83.8	46.8	1.03	2.6	S	0	0	+	0	Polycythemia. VC 48%; MBC 35%
H. F. 43 C.M.	Fullness of pulmon. arc and both pulmon. arts. Pulmon. fibrosis. Cor pulmon.	7	11	—	29	345	556	94.0	—	0.68	2.2	S	+	+	0	0	Polycythemia. Hemat. 66
D. H. 63 W.M.	Pulmon. fibrosis. Emphysema. Cor pulmon. Angiocard; RV hypertrophy	12	—	85/40	57	—	1050	72.3	60.1	1.71	2.6	S	+	+	0	0	Polycythemia. (Expired 5 months after catheter.) No autopsy
A. W. 55 C.M.	Mod. general. card. enlarge. Chron. lung disease	—	18	94/52	71	598	801	63.8	63.8	—	3.5	S	0	+	0	0	Polycythemia. Abnormally tall P waves only in V_1. VC 52%; MBC 36%
R. W. 56 W.M.	Emphysema. Rt. vent. enlarged; left normal.	5	—	53/5*	35†	—	489‡	88.4	50.7	1.65	3.8	S	0	0	+	0	No polycythemia
C. C. 40 W.M.	Chron. lung disease with emphysema. Cor pulmon.	—	—	145/60	89	—	—	48.6	90.3	—	—	S	0	+	0	0	Autopsy: Emphysema. Cor pulmon. RV: 15 mm. LV: 18 mm.
J. Sh. 54 W.M.	Emphysema. Large pulmon. art. Cor pulmon.	4	—	56/34	40	—	651	81.3	52.1	1.57	3.0	S	+	+	0	0	No polycythemia
G. An. 60 C.M.	Emphysema. Cor pulmon.	20	19	119/54	74	1336	1798	55.2	40.3	1.41	1.8	S	0	+	+	0	Autopsy: Emphysema; diffuse interstit. pulmon. fibrosis; cor pulmon. RV 5–7 mm.; LV 12 mm.
G. M. 46 W.M.	—	10	—	92/43	63	—	1372	84.7	44.7	1.57	2.1	S	0	+	0	+	Chron. lung disease clinically

For normal values, see References[2, 6, 27, 28, 34]

TABLE 2.—*Continued*

Patients	X-ray	Pressures (mm. Hg)				Resistances (Dynes sec. cm.$^{-5}$)		Art. O_2 Sat. (% of Capacity) 94–100	Art. CO_2 Content (Vol. %) 45–54	RV Work Kg. M./min./M.^{2} 1.2	Cardiac Index (L./min./M.^{2}) 3.1± 0.4	Electrocardiogram					REMARKS
		RA −2 to +5	PC 5–13	PA S/D 11–29/4–13	PA Mean 8–19	PAR 47–160	TPR 125–250					Rhythm	Abn. P WAVES	RVH	IRBBB	CRBBB	
R. P. 64 C. M.	Chron. lung disease. Cor pulmon. Miliary infiltrate.	12	—	45–62/4–10*	45†	—	1171‡	76.9	64.2	0.91	1.96	S	+	0	+	0	ECG 18 months after catheter. showed both RVH & IRBBB. Died 2 yrs. after catheter. No autopsy
D. M. 46 W.M.	Prom. pulmon. art. Card. enlarge. Cor pulmon.	10	8	70/26	42	466	576	88.1	41.8	1.35	2.9	S	0	0	+	0	VC 106%; MBC 129%. Autopsy: Chron. interstit. pneumonitis.
J. D. 67 W.M.	Chron. lung disease. Mod. card. enlarge.	—	—	34/23	23	—	276	85.9	51.9	—	3.1	S	0	0	+	0	Polycythemia. Hemat.: 59. VC 105%; MBC 51%
J. L. 55 W.M.	Cystic bronchiect., LUL, and LLL	—	—	52/32	35	—	269	72.7	62.4	—	6.5	S	0	0	+	0	VC 43%; MBC 20%. Spirogram typical of emphysema
H. Sa. 59 C.M.	Pulmon. congest. Prominence of pulmon. art. segment. Fibrotic infiltrate in LUL	12	—	82/39	50	—	1573	65.7	62.1	0.88	1.6	S	+	0	+	0	Marked emphysema clinically with almost fixed rib cage. VC 60%; MBC 39%

Abbreviations as table 1.
*†‡See table 1.

right bundle-branch block, complete or incomplete (8 cases); and group IV, those with only incomplete right bundle-branch block and no right ventricular hypertrophy (7 cases).

A statistical comparison* was made between the means of the various groups for the following items: mean pulmonary artery pressure, total pulmonary resistance, arterial oxygen saturation, right ventricular work, arterial carbon dioxide content, and cardiac output. A summary of these results is presented in table 3.

A significant difference was demonstrated between the means of group I and group II for mean pulmonary artery pressure ($p < 0.001$), total pulmonary resistance ($p > 0.001 < 0.01$), arterial oxygen saturation ($p > 0.01 < 0.02$), and level of right ventricular work ($p > 0.02 < 0.05$). No significant difference was demonstrated between the means of arterial carbon dioxide content ($p > 0.9$) or of cardiac index ($p > 0.8 < 0.9$) (table 3).

Groups I and III were compared and a statistically significant difference was found between the means of the two groups for mean pulmonary artery pressure ($p < 0.001$), total pulmonary resistance ($p < 0.001$), arterial oxygen saturation ($p > 0.001 < 0.01$), and right ventricular work ($p > 0.02 < 0.05$). No significant difference was found for the mean arterial carbon dioxide content ($p > 0.6 < 0.7$), or the mean cardiac index ($p > 0.1 < 0.2$) (table 3).

A significant difference was demonstrated between the means of group I and group IV for mean pulmonary artery pressure ($p > 0.001 < 0.01$). No statistically significant dif-

* Standard statistical methods were used throughout.[15, 29]

TABLE 3.—*Statistical Comparison between the Means of Various Physiologic Measurements in Twenty-eight Patients with Chronic Cor Pulmonale*

Physiologi Measurements	Group I No RVH or RBBB (13 Cases)		Group II RVH and/or RBBB (15 Cases)		Group III RVH or RVH and RBBB (8 Cases)		Group IV IRBBB (7 Cases)		Statist. Compar. of Diff. between Group Means t			
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Group I Group II	Group I Group III	Group I Group IV	Group III Group IV
Mean PA pressure (mm. Hg)	26.7	±6.3	49.9	±18.5	60.1	±19.0	38.1	±8.6	4.30‡	5.94‡	3.43†	2.8*
Total pulmon. resistance (dynes sec. cm./$^{-5}$)	448	±130	914	±481	1100	±463	728	±484	3.37†	4.83‡	1.99	1.4
Art. O_2 saturation (% of capacity)	86.0	±8.5	74.2	±14.4	68.9	±16.8	80.2	±8.7	2.60*	3.12†	1.46	1.6
Rt. vent. work (Kg.M./min./M.^{2})	0.95	±0.33	1.28	±0.35	1.37	±0.4	1.16	±0.33	2.23*	2.39*	1.20	.9
CO_2 content (vols. %)	56.7	±7.2	56.9	±13.0	59.6	±16.6	54.3	±8.7	.06	.50	.62	.7
Card. index (L./min./M.^{2})	2.9	±0.7	2.8	±1.2	2.5	±0.6	3.2	±1.6	.23	1.50	.57	1.1

RBBB: Right bundle branch block, complete or incomplete; IRBBB: Incomplete right bundle branch block; RVH: Right ventricular hypertrophy.

Significant probabilities are designated as follows: * 0.05–0.01; † 0.01–0.001; ‡ 0.001.

ference was demonstrated between the two groups for mean total pulmonary resistance ($p > 0.05 < 0.1$), arterial oxygen saturation ($p > 0.1 < 0.2$), right ventricular work ($p > 0.2 < 0.3$), arterial carbon dioxide content ($p > 0.5 < 0.6$), or cardiac index ($p > 0.6 < 0.7$) (table 3).

Finally, group III and group IV were compared. There was a significant difference found between the means of the two groups for mean pulmonary artery pressure ($p > 0.01 < 0.02$). No statistically significant difference was found for total pulmonary resistance ($p > 0.1 < 0.2$), arterial oxygen saturation ($p > 0.1 < 0.2$), right ventricular work ($p > 0.3 < 0.4$), arterial carbon dioxide content ($p > 0.4 < 0.5$) or cardiac index ($p > 0.2 < 0.3$) (table 3).

Part II

A correlation between right ventricular work and (1) the height of the R wave in millimeters in V_1, and (2) the R to S ratio in V_1 was carried out. A correlation of borderline significance was found between right ventricular work and the height of the R wave in V_1 ($r = 0.423$, $p = 0.05$). No significant correlation was found between right ventricular work and the R to S ratio in V_1 ($r = 0.347$, $p > 0.1$).

Part III

Our cases were next classified into three groups. (See fig. 1.)

Group A: Patients with the mean pulmonary artery pressure less than 30 mm. Hg and the total pulmonary resistance less than 750 dynes seconds cm.$^{-5}$ (fig. 1). There were 12 patients in this group. Ten showed no electrocardiographic evidence of right ventricular hypertrophy. One (J. D.) showed the pattern of incomplete right bundle-branch block and one (H. F.) the pattern of right ventricular hypertrophy.

Group B: Patients with the mean pulmonary artery pressure greater than 30 mm. Hg and the total pulmonary resistance less than 750 dynes seconds cm.$^{-5}$ (fig. 1). There were eight patients in this group. One showed the pattern of right ventricular hypertrophy, four showed incomplete right bundle-branch block, and three showed neither right ventricular hypertrophy nor bundle-branch block.

Group C: Patients with the mean pulmonary artery pressure greater than 30 mm. Hg and the

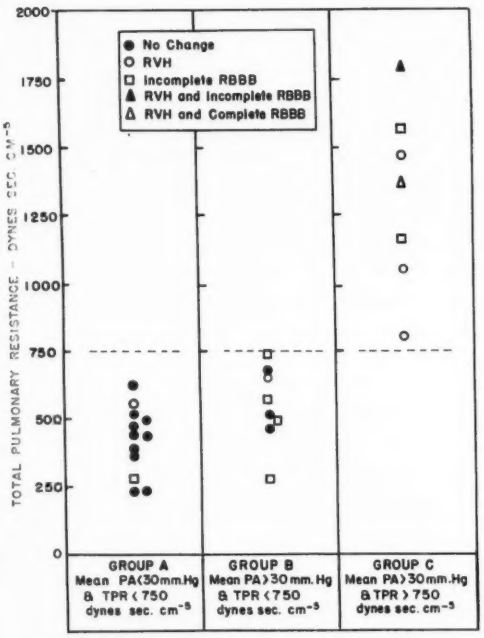

FIG. 1. Relation of mean pulmonary artery pressure and total pulmonary resistance to the electrocardiographic pattern of right ventricular hypertrophy in patients with chronic cor pulmonale. Modified from Dexter and co-workers.[2]

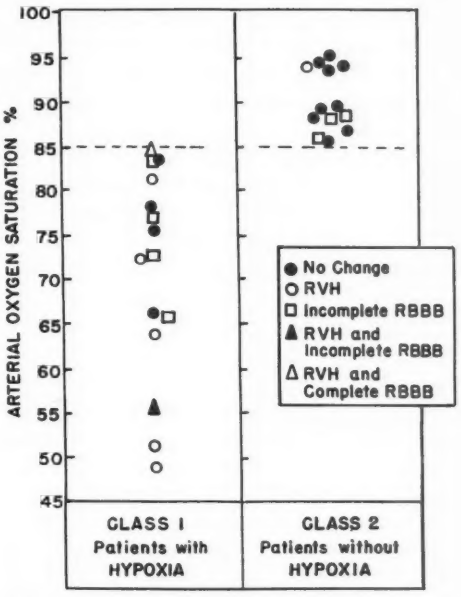

FIG. 2. Relation of hypoxia to the electrocardiographic pattern of right ventricular hypertrophy in patients with chronic cor pulmonale. Modified from Dexter and co-workers.[2]

total pulmonary resistance greater than 750 dynes seconds cm.$^{-5}$ (*fig. 1*). Seven patients were in this group. Three showed the pattern of right ventricular hypertrophy, one exhibited incomplete right bundle-branch block and right ventricular hypertrophy, one showed complete right bundle-branch block plus right ventricular hypertrophy, and two showed incomplete right bundle-branch block.

Part IV

The patients were next divided into two categories: (1) those with hypoxia (arterial oxygen saturation less than 85 per cent) and (2) those without significant hypoxia (arterial oxygen saturation above 85 per cent).[2, 18]

There were 15 patients in the first class and 13 patients in the second class (fig. 2). Eleven of the 15 patients in class 1 demonstrated right ventricular hypertrophy or right bundle-branch block (complete or incomplete). Only 4 of the 13 patients in class 2 showed right ventricular hypertrophy or incomplete right bundle-branch block.

Discussion

Our findings confirm those of Johnson and associates.[1] All of our cases, except one, with the pattern of right ventricular hypertrophy, had a mean pulmonary artery pressure greater than 30 mm. Hg. (The exception, H. F., had a pressure of 29 mm. Hg.) On the other hand, like Johnson and associates, we also had several patients (three in our series) with mean pulmonary artery pressures greater than 30 mm. Hg who did not have the pattern of right ventricular hypertrophy.

All of our cases whose total pulmonary resistance exceeded 750 dynes seconds cm.$^{-5}$ had right ventricular hypertrophy, or right bundle-branch block (complete or incomplete) as did those of Dexter and co-workers.[2] However, there were two cases of right ventricular hypertrophy and five of incomplete right bundle-branch block whose total pulmonary resistance was less than 750 dynes seconds cm.$^{-5}$

All of our seven cases whose total pulmonary resistance exceeded 750 dynes seconds cm.$^{-5}$ had high mean pulmonary artery pressures (50 mm. Hg or greater), and all except one had low cardiac indices. These patients had advanced cor pulmonale.

Of interest is the high incidence of right ventricular hypertrophy in those patients with hypoxia. The reason appears to be that the patients with hypoxia usually have more advanced lung disease. It has been repeatedly pointed out that hypoxia tends to increase the pulmonary artery pressure.[16–19, 24] There was a highly significant negative correlation in the present study between the mean pulmonary artery pressures and the arterial oxygen saturation ($r = -0.799$, $p < 0.001$). This has also been pointed out by other workers in cases of chronic cor pulmonale.[19, 20]

We did not find the close correlation between increasing levels of right ventricular work and the height of the R wave in V_1 and the R to S ratio found by Cosby and co-workers in their cases of congenital heart disease and of mitral stenosis.[7a, b] We did find, however, as they did in their cases of mitral stenosis, that the electrocardiogram was often normal at levels of right ventricular work above 1 kilogram meter per minute per square meter of body surface area.

Of interest was the relative rarity of auricular fibrillation in this series (one case out of 28) as contrasted with its frequency in a similar study[21] of patients with mitral stenosis (11 cases out of 32). This feature of cor pulmonale has already been emphasized.[22]

It has also been pointed out that hypercapnia may be of importance in the development of pulmonary hypertension.[19, 20] Yu and co-workers[19] and Harvey and associates[20] have demonstrated a highly significant correlation between the arterial carbon dioxide tension and the mean pulmonary artery pressure. In the present study we were unable to demonstrate a significant correlation between the arterial carbon dioxide content and the mean pulmonary artery pressure ($r = 0.365$, $p > 0.05 < 0.1$) and no significant difference between the mean arterial carbon dioxide content in those patients without right ventricular hypertrophy and those patients with right ventricular hypertrophy ($p > 0.6 < 0.7$). We have no satisfactory explanation for this discrepancy between our findings and those of these other workers.[19, 20] Stroud and Rahn[6] also failed to demonstrate any significant increase in pulmonary artery pressure or resistance in anesthetized dogs subjected to 5 per cent carbon dioxide in the inspired gas mixture.

Our study confirms the statement of Dexter and his group[2] that, when the electrocardiogram demonstrates the pattern of right ventricular hypertrophy in cases of chronic cor pulmonale, the disease is far advanced. This is borne out by the significantly different mean values for such measurements as mean pulmonary artery pressure, total pulmonary resistance, arterial oxygen saturation and right ventricular work in groups I and III. On the other hand the significance of the occurrence of the pattern of incomplete right bundle-branch block (without right ventricular hypertrophy) is more difficult to assess. Table 3 indicates that the mean values of the above measurements for group IV are intermediate between those of groups I and III. There are no statistically significant differences between the means of these measurements in groups I and IV and groups III and IV except in the case of mean pulmonary artery pressure. The electrophysiologic explanation of the rSR′ pattern in V_1 remains controversial, some workers believing that it is a phase in the development of right ventricular hypertrophy and others that it is due to a conduction defect in the right bundle.[1, 7a, 7b, 8, 25, 26] It is likely that either explanation may be correct depending upon the underlying pathologic process. When this pattern occurs in chronic cor pulmonale, our data favor the former explanation. However, a larger number of cases would be required to establish our results on a firm statistical basis. As in our patients with chronic cor pulmonale, Cosby and co-workers[7a, 7b] have shown that in mitral stenosis and congenital heart disease, incomplete right bundle-branch block may occur at all levels of mean pulmonary artery pressure and pulmonary resistance. This is not surprising when it is re-

called that incomplete right bundle-branch block is a purely electrocardiographic diagnosis which may be demonstrated by an individual whose heart is normal according to all other criteria. However, the presence of incomplete right bundle-branch block, particularly in a young individual without coronary artery disease, should always lead to the consideration of the possibility of a condition associated with increased pulmonary artery pressure.

Summary and Conclusions

(1) Twenty-eight patients with pulmonary hypertension secondary to chronic lung disease have been studied by cardiac catheterization.

(2) Thirteen patients did not show the electrocardiographic pattern of either right ventricular hypertrophy, or right bundle-branch block; 15 patients showed right ventricular hypertrophy and/or right bundle-branch block (complete or incomplete).

(3) A statistically significant difference was demonstrated between the means of these two groups for the following physiologic measurements: mean pulmonary artery pressure, total pulmonary resistance, arterial oxygen saturation, and right ventricular work.

(4) All cases except one with the pattern of right ventricular hypertrophy had a mean pulmonary artery pressure greater than 30 mm. Hg.

(5) All cases whose total pulmonary resistance exceeded 750 dynes seconds cm.$^{-5}$ showed the electrocardiographic pattern of right ventricular hypertrophy or right bundle branch block (complete or incomplete).

(6) The development of the pattern of right ventricular hypertrophy in patients with chronic cor pulmonale usually indicates an advanced state of the disease.

Summario e Conclusiones in Interlingua

(1) Esseva studiate per catheterisation cardiac 28 patientes con hypertension pulmonar secundari a chronic morbo del pulmones.

(2) In 13 del casos nulle configuration electrocardiographic characteristic de hypertrophia dexteroventricular o de bloco de branca dextere esseva observate. Le remanente 15 casos exhibiva hypertrophia dexteroventricular e/o bloco de branca dextere (o complete o incomplete).

(3) Esseva constatate in le duo gruppos differentias de signification statistic inter le valores median pro le sequente mesurationes physiologic: pression pulmono-arterial, resistentia pulmonar total, saturation oxygenic arterial, e labor dexteroventricular.

(4) Omne casos—con le exception de un que exhibiva le configuration characteristic de hypertrophia dexteroventricular—habeva un valor median del pression pulmono-arterial de plus que 30 mm Hg.

(5) Omne le casos con un resistentia pulmonar total de plus que 750 dynas/sec/cm^{-5} exhibiva un configuration electrocardiographic characteristic de hypertrophia dexteroventricular o bloco de branca dextere (o complete o partial).

(6) Le disveloppamento del configuration de hypertrophia dexteroventircular in patientes con chronic *cor pulmonale* indica generalmente un avantiate stadio del morbo.

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Measurement and Significance of Cancellation Potentials on the Human Subject

By ERNEST FRANK, PH.D.

A versatile four-electrode single-channel system is described which is useful for precise research measurements of mirror patterns on the intact human subject, and the theoretic significance of results obtained on normal subjects for the QRS complex is presented in detail. It is concluded that the QRS complex at all points on the body of normal human subjects, including the precordium, can be considered to arise from a fixed-location equivalent heart dipole to an average accuracy of 5 per cent. Therefore, the "proximity" potential concept is untenable for the normal QRS complex.

THE degree to which electrical activity of the human heart may be represented by a dipole has been an important issue in electrocardiography for the past half century. The question of relative "electrical remoteness" of electrodes placed at various points on the body surface has often been debated, and, in particular, whether "proximity" potentials[1] (owing to physical closeness to the heart) on the precordium are real or apparent.[2] An associated question attending the dipole hypothesis concerns the degree to which the dipole location remains fixed during heart-muscle electrical activity. Despite their importance, these questions are unresolved to this day. However, pertinent evidence can be obtained by direct experiments on humans, both normal and abnormal, using a precision cancellation technic requiring a simple preamplifier in conjunction with a standard single-channel electrocardiograph. It is the purpose of this paper to describe methods, apparatus and techniques for performing cancellation experiments on humans and to discuss their significance.

The existence of mirror patterns on the human subject may be readily shown qualitatively by recording heart signals at a given point on the body surface and then finding some other body-surface point which gives a signal of the same instantaneous waveform but opposite in polarity, and usually of different amplitude. Both signals are recorded with respect to some fixed reference point; usually the Wilson central terminal. While conventional mirror patterns give a qualitative idea of the potential distribution on the human torso, they are of questionable quantitative significance in view of the false mirror patterns[3] that can be observed. The cancellation technic to be described is, essentially, the application of a null technique, inherently capable of high precision, to the study of mirror patterns in fine detail. Application of this technic leads to quantitative results which have significance with respect to the fixed-location dipole representation of heart activity. The experimental method and procedure extends the work of Schmitt and associates[3] by taking a more general view of cancellation rather than restricting it to the Wilson central terminal, and also employs simple equipment within reach of any research electrocardiographer. The theoretical foundation of the method is an extension of the works of Burger and van Milaan,[4] and can be interpreted geometrically in accordance with the image surface viewpoint, as shown in appendix I. It is hoped that both the generality of the method as well as the reasonable equipment requirements will stimulate cancellation experiments on such a scale as to establish to the satisfaction of all a quantitative measure of the degree to which the fixed-location dipole hypothesis is applicable to humans.

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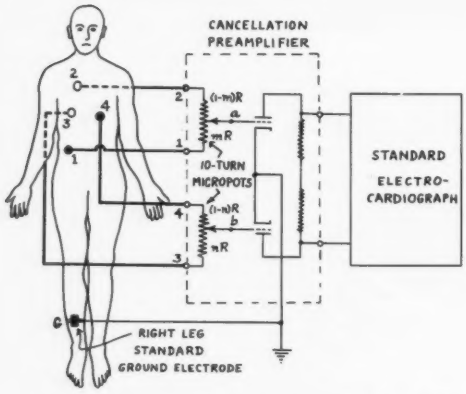

FIG. 1. Experimental arrangement for cancellation measurements. Flat disc electrodes 1, 2, 3, 4 may be conveniently affixed in the desired locations with adhesive tape. Black circles indicate front electrodes; white circles rear electrodes. The subject may assume any fixed posture. The preamplifier, described in detail in appendix III, contains two precision 100,000 ohm, 10-turn micropots (potentiometers) at its input. The preamplifier output is connected to a standard electrocardiograph such as a Sanborn single-channel Viso Cardiette.

EXPERIMENTAL METHOD

Null technics have been used widely in many fields where precision is a requirement. The chemical balance, for example, is essentially a null device in which zero deflection of the balance indicator is the criterion for equality of weights. There are thousands of devices of this type which generally possess the advantages of high precision, high sensitivity and accuracy relatively independent of the characteristics of the null indicator. Electric measurements employing null technics are usually called bridge measurements in which a zero or minimum indication of a detector enables deductions concerning elements in the bridge circuit.

Electric null technics may be applied to the human subject in a variety of ways. One method has been discussed in detail.[3] The method to be presented here is more general and entails the use of two electrode pairs affixed to the human torso with potentiometers (micropots) connected between the electrodes as indicated in figure 1. The objective is to seek combinations of electrode locations and potentiometer settings such that a potential difference approaching zero is established between the two sliding taps of the potentiometers. This phenomenon, called "cancellation", is an extremely sharply defined condition experimentally. The electrodes 1, 2, 3, 4 need not be confined to any particular sites and there is no requirement that the anatomic lines joining the electrodes pass anatomically through or even near the heart. Indeed, when cancellation is obtained the anatomic lines joining the electrodes will not even intersect each other.

At first sight it might appear from figure 1 to be hopelessly difficult to obtain cancellation because of the large number of variables (four electrode locations and two potentiometer settings) at the disposal of the experimenter. However, a systematic cancellation-search procedure may be devised as follows: Electrodes 1, 2 and 4 may be initially fixed at arbitrary locations and the setting of the potentiometer joining electrodes 1 and 2 may be fixed. Then, with the remaining two variables it is usually possible to obtain cancellation by trial on different locations of electrode 3, varying the setting of the potentiometer connected from 3 to 4 for each trial location of electrode 3. The tap of the potentiometer joining electrodes 1 and 2 may be regarded as an arbitrarily fixed reference potential. (It need not be at the electrical center of the heart to obtain cancellation.) The potential from electrode 3 to this tap should be an exact mirror pattern (except for amplitude) of the potential from electrode 4 to this tap to obtain perfect cancellation, and this can serve as a guide to trial search locations of electrode 3. Frequently as much as one hour of cancellation search is required before the best cancellation is obtained.

Practical difficulties attending cancellation measurements of this type on the human subject are not to be minimized and may be placed conveniently in two categories: control of parameters and control of sources of variable error.

Control of Parameters. The parameters of the electrical system comprised of heart and body must be held constant if sensible measurements are to be performed. Exactly the same respiratory state (insofar as is practicable) should exist throughout the cancellation attempt. The anatomic location of the heart, even though changed only slightly by normal breathing, is a factor of major importance in influencing body-surface potentials,[5, 6] especially when potential differences of less than 0.1 millivolt are being measured. Posture should be maintained as constant as practicable throughout each cancellation attempt. While some electrode sites are relatively insensitive to posture changes, others are affected pronouncedly by slight shifts of body position.

Control of Sources of Variable Error. There are certain sources of error which can introduce difficulties if they are allowed to fluctuate. The skin must be rubbed thoroughly before affixing the electrode in order to achieve low electrode polarization impedance. If this impedance is low, it can change somewhat without causing ill effects, and also helps to minimize 60 cps interference. A direct current ohmmeter may be employed as a rough measure of electrode resistance, which should be small compared with the 100K potentiometers. (See appendix

III.) It is desirable to use the smallest size electrodes compatible with low polarization impedance in order to obtain sharply defined nulls with respect to body-surface locations of electrodes. Although standard size precordial electrodes are too large for highly precise work, they may be used if only cancellation existence is to be shown. For precise delineation of body-surface points which produce cancellation, 27 gage hypodermic needles or ¼ inch diameter electroencephalograph electrodes give good results, but one-half inch or ⅝ inch diameter disc electrodes are also satisfactory. Contiguity of electrode jelly must be avoided. Reproducibility of electrode placement is a critical factor, depending upon both electrode size and location, but is not a major concern if the objective is only to demonstrate cancellation existence in a given instance. Electrodes should be fixed firmly during each cancellation attempt. Despite these obstacles, the development of good techniques leads to accurate, conclusive results.

Typical Experimental Results

Schmitt and associates[3] have presented detailed reports of cancellation experiments with respect to the Wilson central terminal on human subjects with normal and diseased hearts. Although they did not employ the four-electrode system of figure 1, the same principles of cancellation discussed here are applicable to their studies. Their erroneous contentions that cancellation is dependent upon the Wilson central terminal being at the electrical center of the heart and that anatomic lines joining the electrode locations which produce cancellation must cross through the anatomic heart center in no way invalidates their experimental observations of cancellations, or their interpretation of the significance of cancellation as a measure of the validity of the dipole hypothesis.

The four-electrode system of figure 1 has been applied to several normal subjects and QRS-complex cancellations have been obtained from a wide variety of electrode sites.* Most of these entailed the application of at least one electrode, and in many cases two electrodes, on the precordium in close anatomic proximity to the heart. The existence of QRS-complex cancellations on normal human subjects has

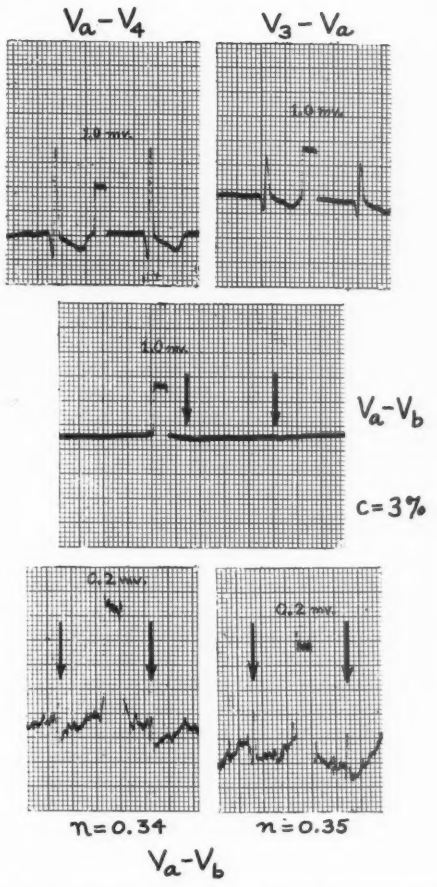

Fig. 2. Typical example of mirror patterns and cancellation potentials for the QRS complex in a normal male subject. The upper records show potential differences of electrodes 3 and 4 with respect to tap *a* of the potentiometer joining electrodes 1 and 2 at the usual standardization used in clinical electrocardiography. These potential differences are nearly exact mirror patterns; one is recorded with reversed polarity for convenience in comparing wave shapes. The potential difference between potentiometer taps *a* and *b* is also shown at normal standardization in the middle record. The arrows indicate the noncancelling portion of the QRS complex which is barely discernible, and shows the need for increased amplification. The lower records, using approximately 10 times the usual amplification, enable a quantitative measure of the residual voltage which has its smallest value with a potentiometer setting of $n = 0.34$. With $n = 0.35$ the residual voltage is significantly larger and is a typical example of the criticalness of the potentiometer setting and the extreme sharpness of the cancellation phenomena.

* The author is indebted to Dr. Paul H. Langner, Jr. for some of these results and also for the use of facilities of the Provident Mutual Life Insurance Company, Philadelphia, Pa. while establishing equipment requirements and techniques for the cancellation method.

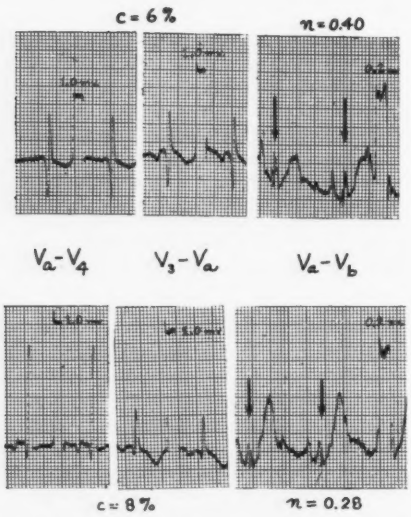

FIG. 3. Mirror patterns and cancellation potentials for the QRS complex in a normal male subject in cases where the P and T wave cancellation is far inferior to the QRS cancellation. The arrows indicate the noncancelling portion of the QRS complex in records taken at about ten times normal standardization. In each case one of the mirror patterns has been recorded with reversed polarity so as to obtain potentials of nearly identical shape.

been established irrefutably and can be reproduced accurately for all subjects tested.

A typical example of cancellation records for the QRS complex is given in figure 2. Mirror patterns of electrodes 3 and 4 with respect to potentiometer tap *a*, connected between electrodes 1 and 2, and the residual voltage V_a-V_b, the potential difference between potentiometer taps, are shown at the usual standardization. The residual votage is almost imperceptible and illustrates the need for additional amplification provided by the preamplifier. The amplified residual may also be seen in figure 2 where a potentiometer setting of $n = 0.34$ results in a minimum residual voltage of approximately 50 microvolts, which is a direct quantitative measure of the differences in shape and timing of the two patterns.

In general, when cancellation is obtained for the QRS complex, neither the P nor T waves cancel to the same degree, signifying either that the center of electrical activity for these last complexes differs from that of the QRS or that the degree to which the dipole hypothesis applies is different. Two representative cases showing noncancelling P and T waves are given in figure 3. In the lower case illustrated the noncancelling portion of the T wave is seen to be far in excess of the QRS residual voltage despite the fact that the T wave itself is small compared with the QRS complex.

The degree of cancellation may be described quantitatively by a cancellation coefficient, as discussed in detail in appendix II, which involves the potential differences across electrode pairs 1-2 and 3-4, and the residual or uncancelling portion of the heart signals. In the records of figure 2, the cancellation coefficient is 3 per cent which signifies that 97 per cent of the potentials at any of the four electrodes can be explained by postulating an equivalent heart dipole, assuming each electrode contains approximately the same percentage of nondipolar potential. If one electrode is assumed to be entirely responsible for the residual potential, with the remaining three electrodes all perfectly dipolar, the per cent cancellation coefficient indicates approximately one half the per cent nondipolar potential. Cancellation coefficients of 6 per cent and 8 per cent are illustrated in figure 3. The histogram in figure 4 shows 38 cancellation coefficients for the QRS complex obtained on one normal male subject from various electrode locations distributed over the entire torso. No correlation between electrode location and quality of cancellation was observed; precordial potentials were explainable by the dipole hypothesis equally well as those of anatomically distant electrodes.

The theoretical basis for cancellation presented in appendix I reveals that the existence and quality of cancellation does not rely upon anatomic lines crossing through the heart, nor upon the potential difference between the potentiometer taps and the electrical center of the heart, contrary to the claims of Schmitt and associates.[3] This can be demonstrated readily by direct experiment. For example, electrodes 1, 2 and 4 may be fixed in position as shown in figure 5, with electrode 4 on the precordium directly over the heart. With the 1-2 potentiometer set to position a_1 (mid-position), a location of electrode 3 somewhere on the back

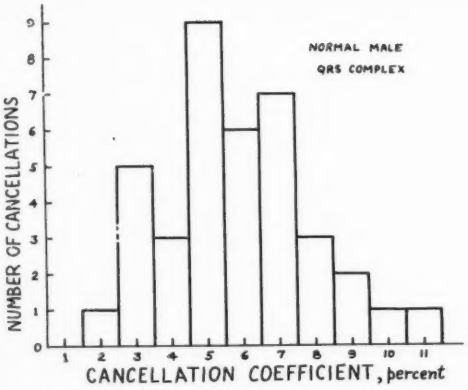

FIG. 4. The results of extensive QRS cancellation measurements on a single normal male subject are shown in terms of cancellation coefficients for 38 separate and independent trials. These data represent approximately 60 hours of experimental time using 27 gage hypodermic needle electrodes. In all cases at least one electrode was on the precordium but other electrodes were located at a wide variety of points over the entire torso. The mean cancellation coefficient is 5.8 per cent with a standard deviation of ±2 per cent. Two cases which were more than 3 standard deviations away from the mean were discarded.

can be found such that cancellation is obtained when the 3-4 potentiometer is appropriately adjusted. Then the 1-2 potentiometer setting may be changed to either a_2 or a_3 (leaving electrodes 1, 2 and 4 unchanged) and different electrode 3 locations (and 3-4 potentiometer settings) for cancellation will be obtained as indicated schematically in figure 5. Several experiments of this type have been performed and there is no significant difference in the quality of cancellation for the various conditions, despite the fact that the potentiometer junctions are at widely different potentials in each case and the lines joining the electrodes differ markedly in each case. This is exactly what is expected from theoretical considerations. Indeed, if the quality of cancellation did depend upon the degree to which the potentiometer taps approach the electric center of the heart, this would be fortunate for it would then provide a precision method for determining the electrical center of the heart. Instead, the electric center of the heart proves to be a much more evasive quantity and is not determinable by so simple a means. There is a method, however, taking advantage of the precision of the cancellation technic itself, which can be devised to determine the location of the center of electric activity of the human heart with remarkable accuracy.[7]

Many salient features of cancellation experiments have been discussed by Schmitt.[3] The experimental definition of the potentiometer settings is extremely sharp; changes of 2 per cent may be detected readily in typical cases (fig. 2). However, in special cases where the potentiometer joins electrodes displaying small transitional complexes, a situation which can be encountered when the QRS loop is nearly in a plane, the potentiometer setting can become relatively insensitive. If small electrodes are used, changes in anatomic location of one electrode by as little as ½ inch produces measurable effects as cancellation is approached, but this depends considerably on the region of the torso being explored. Usually, the right side and back are not as critical of elec-

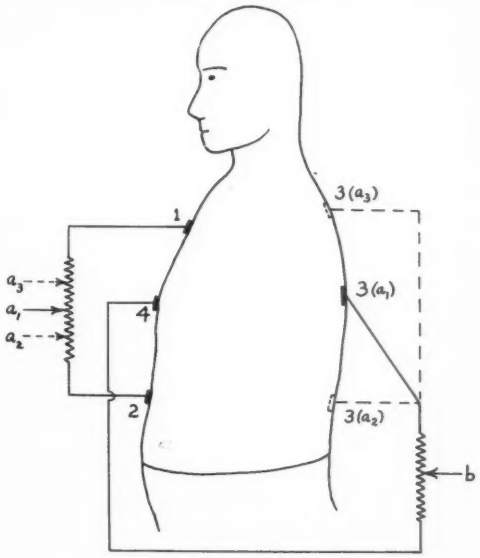

FIG. 5. Experimental arrangement of four-electrode system of figure 1 useful in demonstrating that existence and quality of cancellation does not depend upon potentiometer-tap potentials with respect to the electrical center of the heart, nor upon the notion that anatomic lines joining electrodes must pass through the anatomic center of the heart. See text for discussion.

trode placement as the rest of the torso, but this depends to some extent on heart eccentricity and the specific dipole variations of the subject under test. The highly sensitive nature of these experiments is indicative of their inherent precision capabilities, and underscores the need for careful control of respiration, posture and other disturbing influences.

Significance of Cancellations

The theoretical significance of experimentally observed cancellations on the human subject, which unquestionably exist for the QRS complex in normals, is presented in quantitative mathematical terms in appendix I. Before discussing cancellation significance, one important point should be emphasized. The basic electrical phenomenon involved is the existence of mirror patterns. The four-electrode system of figure 1, the system of Schmitt,[3] or any other cancellation systems that may be devised merely represent precision technics designed to measure the degree of mirrorness with high accuracy and objectivity. The success of the technic relies on the principle of examining directly the *difference* between two wave shapes, automatically compensating for their unequal amplitudes, rather than examining the wave forms themselves. A distinction must be made between the technic and the phenomenon. By the use of this technic it may be said that two wave forms are mirror images to within a certain per cent, very accurately defined by direct experiment. Hence, the question that must be answered is, really, what is the significance of exact or nearly exact mirror patterns on the human subject?

Generally speaking, an hypothesis or theory is a logical set of ideas which may be used to account for experimental observations. A theory is useful so long as it can explain all the experimental phenomena (to an accuracy sufficient for the problem) which fall into its province. Such a theory enables prediction, given a set of conditions, and therein lies one of its major values. There is, however, nothing fundamentally unique about a theory; a group of different theories might all yield explanations and predictions of comparable accuracy. Of all possible theories, however, the usual choice in science is the simplest one. Thus, in discussing the significance of cancellation, one approach is to propose the simplest theory which would have predicted cancellation and which is also consistent with other known observable experimental phenomena concerning body-surface potentials on the human subject. If a theory is constructed which represents the electrical effects in the human heart by a fixed-location dipole, it can be predicted from this theory that perfect cancellations will be found. Hence, the degree to which cancellations exist experimentally constitutes a measure of the accuracy of the fixed-dipole theory. It is imperative to recognize that no claim is made that the heart *is* a dipole; indeed, this is known to be untrue. But, insofar as the potentials produced at the body surface are mirror patterns, the heart may be represented by a dipole.

Assumptions in addition to the fixed-location dipole are obviously required to develop a complete theory for the human heart-body electrical system, since the medium characteristics play an important role, and these assumptions must not be contrary to known observations. It is reasonable to assume that the conducting medium is finite and has a boundary shape the same as that of the human body; that the fixed location of the equivalent heart dipole is not restricted to any particular point within the chest, since it is to be expected that different individuals will have different heart locations; that the medium is not necessarily homogeneous but, for simplicity, it is assumed to be linear and resistive. None of these assumptions violate the prediction of cancellation. However, the existence of cancellation does not validate these additional assumptions. For example, cancellation would be predicted from a theory which postulated either a homogeneous or an inhomogeneous conducting medium; thus, the existence of cancellation in itself sheds no light on the homogeneity question. Again, cancellation would be predicted for any fixed location of the equivalent dipole within the medium and hence the existence of cancellation cannot in itself reveal information about the dipole location. Since a general theory has not yet been developed for the case of a nonuniform reactive medium, or a nonlinear medium, it cannot be stated conclusively at this time whether or not cancellation would still be predicted in such systems. Certain qualitative reasoning indicates that cancellation would not be expected in such media, but this has not been established rigorously. Fortunately, this question is not important for the present, since the simplest theories should be exploited fully and only made more complicated when

experimental evidence demands that they be changed. However, the minute current density in the human torso resulting from heart action suggests that the linearity assumption is applicable. Moreover, it has been shown in dogs that the medium phase shift is negligible at heart frequencies,[8] indicating that the resistive assumption is probably accurately applicable to humans.

Summarizing, the simplest complete theory which accounts for exact or nearly exact mirror patterns on the human subject, which at the same time does not place unrealistic restrictions on the rest of the system, is one in which heart activity is represented by an equivalent dipole fixed in location in an inhomogeneous resistive linear medium with a boundary the same as the human figure.

In terms of this hypothesis, the cancellation coefficient gives a measure of the maximum percentage error with which heart action may be described in terms of an equivalent dipole. It gives a maximum limit because several factors in addition to the nondipolar behavior of the heart contribute to the measured residual voltage. For example, changes in location of the dipole during the measurement give rise to a residual voltage even though heart action itself were perfectly dipolar. The tolerable dipole movement in a typical normal subject is very small; it can be shown[7] that a dipole motion of 0.5 cm., or even less in some cases, can produce a residual voltage equal to that which gives 5 per cent cancellation. Thus, the fixed location is pinned down rather tightly by a small cancellation coefficient. Indeed, it may well be that dipole movement during the QRS complex is responsible for a substantial portion of the residual voltage. A measurable factor, which typically accounts for about 10 per cent of the residual voltage, is the imperfect common-mode rejection of the right leg (ground) signal in the system of figure 1, and is discussed in appendix III. Also, location of the search electrode, despite great care, is never perfect. In addition, inadequate respiration and posture control during cancellation search as well as nonthoroughness of search can account for part of the residual. Atrial depolarization effects may also be present during the QRS complex. In view of all of these factors which may contribute to the residual voltage it is remarkable that such excellent cancellations can be consistently obtained. The contributions of each factor, separately considered, must be small since they could not conceivably compensate for one another for a large number of cancellations obtained from many different widely distributed electrode sites.

Discussion

The accuracy with which the human heart may be represented by an equivalent dipole during the QRS complex, despite its substantial anatomic dimensions compared with the size of the chest and despite its eccentric location within the chest, may be estimated roughly by theoretical analysis. Such an analysis has been presented in detail,[9] in which the boundary potential produced on the surface of a homogeneous resistive sphere by an eccentric, dome-shaped double layer, representing the depolarization wave in the ventricles, was compared with that produced by an equally eccentric dipole. For a representative eccentricity equal to 30 per cent of the sphere radius and for a double-layer diameter equal to 60 per cent of the sphere radius (see fig. 6), it was found that the dipole approximation entails errors of less than 5 per cent for about 97 per cent of the spherical surface, and not more than 10 per cent for the remaining 3 per cent of the surface. While several idealizations are embodied in this analysis, it does include effects of eccentricity and finite boundary, thus improving on previous theoretical attempts at assessing this approximation. The result indicates that the dipole hypothesis seems reasonable during the QRS complex in normals, which indeed is found to be the case experimentally. Other theoretic analyses and statements in the literature which suggest that the dipole hypothesis entails sizeable errors on theoretic grounds have either been interpreted incorrectly or have not taken proper account of the influence of dipole eccentricity and finite boundary.

Quite apart from the mathematic treatment of this problem, it is not unreasonable on qualitative grounds to expect the dipole representation to be applicable, even for precordial potentials. The limb-lead potentials are only about 1 or 2 per cent of the potential difference across the depolarization wave in the myocardium, owing to the internal short-circuiting

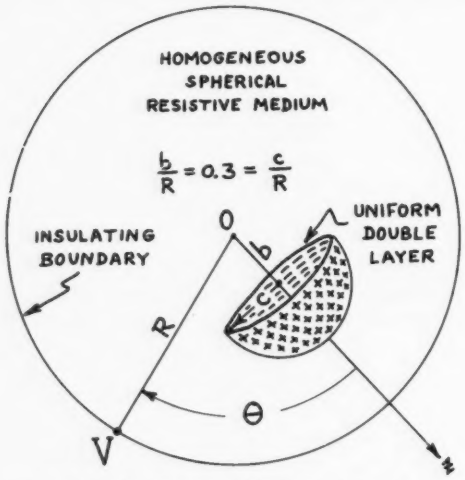

FIG. 6. Scale drawing of idealized theoretic model useful in estimating the degree to which the dipole approximation is applicable to an eccentric uniform dome-shaped double layer representing ventricular depolarization. For the case illustrated, a dipole (of moment equal to that of the double layer) located at the center of the circular rim of the double layer produces a boundary potential V which differs by less than 5 per cent from the double-layer potential except within a cone defined by $\theta = 20°$ where the dipole approximation error rises to 10 per cent. The results of this analysis give theoretic support for experimentally observed cancellations on normal humans which are indicative of heart-dipole behavior.

effects of the torso medium and to the anatomic distance from heart to boundary. This implies that the limbs are in the very distant field of the heart and the dipole representation seems, therefore, quite appropriate. Normal precordial potentials being about 3 to 6 times the magnitude of the limb potentials are still only about 3 to 12 per cent of the double-layer potential difference. This suggests that the dipole representation may still not be seriously in error even for precordial electrodes.

A variety of factors make it understandable in terms of dipole behavior how the "proximity" potential idea could have been falsely deduced on an intuitive basis. The rapid changes in potential with electrode location on the precordium, the larger magnitude of these potentials as compared with limb leads, and the rather sudden changes in shape of the potentials when the precordial electrode is moved only slightly are effects which suggest a proximity type interpretation; yet they are also clearly explainable in terms of dipole behavior. A study of the potentials produced on the precordium by an eccentric dipole indicates that the potential changes extremely rapidly with anatomic distance. An anatomic change of as little as 1 inch corresponds to a change in electrical angle from which the dipole is viewed of about 30 degrees.[10] Thus, for certain dipole variations one might expect rapid changes in both amplitude and shape of pattern, even though the electrode anatomic positions are shifted slightly. Moreover, a study of dipole potentials around the chest at the transverse level of the heart[7] reveals that contributions of the head-to-foot component of the dipole to precordial potentials depends very critically on the up-down location of the electrode. If the electrode is moved up or down slightly, the head-to-foot dipole component which may differ considerably in shape from the other components, may contribute very little or enter rather substantially, with one polarity or the reverse, and could easily account for drastic shape changes. Finally, the matter of localized damage may also be given a sound dipole interpretation, although no claim is made here concerning the degree to which the dipole hypothesis is applicable in such cases. A local area of damage causes the dipole variations to be altered but does not necessarily invalidate the concept that the potentials are still dipolar in nature. Thus, local damage which causes the dipole components to change will produce changes in the precordial (and other) electrode potentials, and the concept of proximity effects may not be necessary. The dipole changes owing to local damage can be shown in many cases to account for apparent proximity potentials; indeed, both concepts might lead to the same conclusion in some cases.[11]

Acceptance of the heart dipole representation rules out the so-called "proximity" potentials for these could not be explained on the basis of dipole behavior. The existence of nearly exact mirror patterns can be seen qualitatively to contradict the proximity potential concept. If proximity potentials did exist, then precordial waveforms would have a significant percentage

of potential traceable to the directly underlying portion of active heart muscle. Nearly identical waveshapes generally would not be found at some other body surface point such as on the back where the proximity effect contributes much less if anything at all. Cancellation would be very poor if substantial proximity effects existed, and the dipole hypothesis would have to be abandoned, at least for precordial electrodes. The fact that in normals the cancellation coefficients are typically 5 per cent for precordial electrodes paired with distant electrodes indicates that the contribution to the total wave form of the proximity potentials cannot be more than 10 per cent, and probably less. It should be clear that the proximity potential concept is untenable unless it can be demonstrated conclusively, using a precision cancellation technic, that it is not possible to obtain a high degree of cancellation in certain subjects using electrodes affixed to the proximity areas. Although this might appear to be unlikely, in view of the results for normals, because diseased hearts are not necessarily characterized by being in closer proximity to the anterior chest, it should be realized that drastic changes in the depolarization process could impair the accuracy of the dipole representation. Indeed, such effects though not very pronounced and perhaps traceable to other factors have been reported.[3] No claim is offered that excellent cancellations would be found in all individuals, normal and abnormal. But precordial QRS cancellation, even in a single individual, demonstrates that dipolar behavior can and does exist, and that in any such individual the concept of "proximity" potentials is groundless for the QRS complex. The breadth of this conclusion remains to be defined.

Cancellations obtained in this laboratory have been restricted to normal subjects and the QRS complex. Schmitt and associates[3] have performed QRS cancellations on patients with heart disease and conclude that the dipole hypothesis is still useful but less accurate than in normals. Application of this technic to the P and T waves has not been attempted in detail and is technically more difficult than QRS cancellations because of the smaller signal amplitudes of the P and T waves and the increased muscle-tremor interference. However, Schmitt's findings that the center of activity of the T wave is not the same as that for the QRS has been confirmed but has not been examined in quantitative detail. If the centers are substantially different, this would have important consequences, requiring a thorough reexamination of ventricular gradient concepts and also of the meaning of comparing QRS and T loop in spatial vectorcardiography when the same recording system is used for both loops.

Summary

A versatile four-electrode single-channel system requiring a simple one-tube preamplifier in conjunction with a standard electrocardiograph is described in detail. Experimental methods and sources of error in the application of this system for precision measurement of mirror patterns on the human subject are discussed. Results of thorough cancellation studies on normal subjects for the QRS complex are presented in terms of a cancellation coefficient which describes the nondipolar content of body-surface potentials. Theoretic significance of cancellation existence is discussed in qualitative and mathematics terms, and previous misinterpretations of cancellation experiments are clarified. It is concluded that the QRS complex at all points on the human torso, including the precordium, for normal subjects can be considered, to an accuracy of 5 per cent, to arise from a fixed-location equivalent heart dipole and, therefore, that the "proximity" potential concept is untenable for the normal QRS complex.

Summario in Interlingua

Es describite in detalio un versatile systema quadrielectrodic a via unic que require un simple preamplificator monotubal in conjunction con un electrocardiographo standard. Es discutite methodos experimental (e lor fontes de errores) pro le application de iste systema al mesuration precise de traciamentos specular ab subjectos human. Resultatos de exacte studios de cancellation pro le complexo QRS in subjectos normal es presentate exprimite per

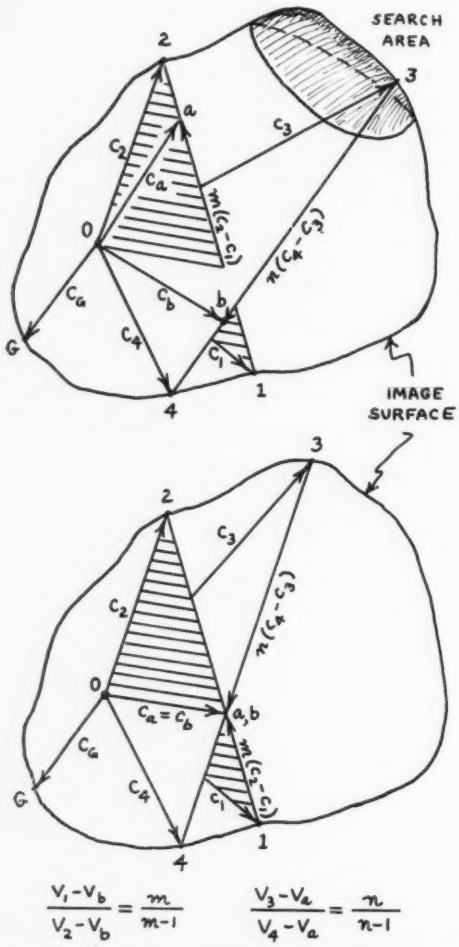

FIG. 7. Geometric representation in image space of the four-electrode cancellation system of fig. 1. The upper figure illustrates the general three-dimensional relationship among the unipolar vectors and the potentiometer taps. Points *a* and *b* can be moved along the vectors c_2–c_1 and c_4–c_3 by varying *m* and *n*, respectively, while the tip of vector c_3 can be moved on the image surface by changing the anatomic location of electrode 3. The lower figure illustrates the condition for perfect cancellation, coincidence of points *a* and *b*.

un coefficiente de cancellation que describe le contento nondipolar de potentiales al superficie del corpore. Le signification theoric es discutite qualitative—e methematicamente, e previe misinterpretationes de experimentos de cancellation es clarificate. Es deducite le conclusion que le complexo QRS in subjectos normal e pro omne punctos del torso human—non excludente le precordio—pote esser considerate, sin plus que 5 pro cento de perdita in exactitude, como originate per un equivalente dipolo cardiac a location fixe. Isto significa que le concepto del potential a "proximitate" es intenibile pro le normal complexo QRS.

ACKNOWLEDGMENTS

The author expresses appreciation for the interest and active participation of Dr. C. F. Kay, Dr. George Seiden and Dr. Robert Keisman, the first of whom served as the subject for the data presented in figure 4. The cancellation preamplifier was constructed by Mr. L. A. Rubin.

APPENDIX I

Theoretic Basis for Cancellation

If a current dipole is fixed in location anywhere within a three-dimensional linear resistive inhomogeneous medium bounded by a perfect insulator of any shape, the potential at any point such as 1 on the boundary may be expressed[12] as a linear combination of the three rectangular components of the dipole vector as follows:

$$V_1 = c_{1x}p_x + c_{1y}p_y + c_{1z}p_z = \mathbf{c}_1 \cdot \mathbf{p} \qquad (1)$$

where $\mathbf{p}$ is the dipole (heart) vector with components p_x, p_y and p_z; c_{1x}, c_{1y} and c_{1z} are constants and components of a vector $\mathbf{c}_1$ which depend upon the medium characteristics (size, shape, resistivity, distribution of inhomogeneities), the location of the dipole and the location of the boundary point 1 at which the unipolar potential is V_1 with respect to the dipole mid-potential, arbitrarily taken as zero. A geometric interpretation of equation (1) is that the scalar unipolar potential V_1 arises from the projection of the time-varying heart vector $\mathbf{p}$ onto the fixed vector $\mathbf{c}_1$ times the length of $\mathbf{c}_1$. For any other boundary point such as 2, $V_2 = \mathbf{c}_2 \cdot \mathbf{p}$ where $\mathbf{c}_2$ is different from $\mathbf{c}_1$ but depends upon similar factors as $\mathbf{c}_1$, and V_2 has a similar geometric interpretation to that of V_1. The anatomic situation showing electrodes 1, 2, 3, 4 and G in figure 1 may be represented geometrically in image space[4, 10, 12] insofar as electric effects are concerned as shown in figure 7 where the unipolar vectors $\mathbf{c}_1$, $\mathbf{c}_2$, $\mathbf{c}_3$, $\mathbf{c}_4$ and $\mathbf{c}_G$ are drawn from a common origin *O*, the dipole mid-potential. These unipolar vectors do not depend upon the particular way in which $\mathbf{p}$ varies with time, provided the location of $\mathbf{p}$ remains stationary.

The potential difference across the potentiometer connected between anatomic points 1 and 2 in figure 1 may be expressed in terms of the unipolar vectors as $V_1 - V_2 = (\mathbf{c}_1 - \mathbf{c}_2) \cdot \mathbf{p}$ provided the potentiometer resistance R is very large compared with the

nedium-plus-skin resistance. Consequently, the potential of the sliding tap a with respect to the lipole mid-potential is

$$V_a = V_1 - \frac{(V_1 - V_2)}{R} mR$$
$$= V_1 (1 - m) + mV_2$$
$$= [\mathbf{c}_1(1 - m) + m\mathbf{c}_2]\cdot\mathbf{p} = \mathbf{c}_a\cdot\mathbf{p}$$

where m is the fractional setting of the potentiometer and $\mathbf{c}_a$ is defined as $\mathbf{c}_a = m(\mathbf{c}_2 - \mathbf{c}_1) + \mathbf{c}_1$. Therefore, as indicated in figure 7, the geometric interpretation of V_a is the projection of $\mathbf{p}$ onto the vector $\mathbf{c}_a$ times the length of $\mathbf{c}_a$, where the tip of the vector $\mathbf{c}_a$ can be moved along the vector $\mathbf{c}_2 - \mathbf{c}_1$ in image space as determined by the potentiometer setting m. The tip of the vector $\mathbf{c}_a$ can be seen to be variable from electrode 1 when $m = 0$ to electrode 2 when $m = 1$. This proves that the locus of the tip of $\mathbf{c}_a$, when m is varied, is a straight line in image space (and, incidentally, constitutes a proof of the "synthetic" lead principle.[13] Thus, the manner in which the potentiometer enables a point to be varied electrically with respect to the dipole mid-potential can be seen geometrically.* Exactly similar reasoning leads to a geometric interpretation of point b, the 3-4 potentiometer junction, in terms of the vector

$$\mathbf{c}_b = n(\mathbf{c}_4 - \mathbf{c}_3) + \mathbf{c}_3$$

shown in figure 7, and $V_b = \mathbf{c}_b\cdot\mathbf{p}$.

The potential difference between points a and b, the sliding taps of the potentiometers, is measured by the arrangement shown in figure 1 and perfect cancellation is defined as the condition under which this potential difference is zero during a given complex. In general, it may be seen in figure 7 that $V_a - V_b$ will not be zero. However, it is obvious from figure 7 and the geometric interpretation that has been presented that the only condition under which cancellation can exist (within the province of this theory) for all values of $\mathbf{p}$ is that the points a and b coincide in image space. Mathematically, the condition for cancellation is $V_a - V_b = 0 = (\mathbf{c}_a - \mathbf{c}_b)\cdot\mathbf{p}$ which can be true for all values of $\mathbf{p}$ only if $\mathbf{c}_a = \mathbf{c}_b$; in other words, points a and b must coincide. Cancellation conditions are portrayed in figure 7. When points a and b coincide (in three-dimensional space) it follows that

$$V_1 - V_b = (\mathbf{c}_1 - \mathbf{c}_b)\cdot\mathbf{p}$$

and $V_2 - V_b = (\mathbf{c}_2 - \mathbf{c}_b)\cdot\mathbf{p}$ are exact mirror patterns because $\mathbf{c}_2 - \mathbf{c}_b = \mathbf{c}_2 - \mathbf{c}_a = (m - 1)(\mathbf{c}_1 - \mathbf{c}_2)$ and $\mathbf{c}_1 - \mathbf{c}_b = \mathbf{c}_1 - \mathbf{c}_a = m(\mathbf{c}_1 - \mathbf{c}_2)$ are vectors in opposite directions ($m \leqq 1$). In fact, under conditions of perfect cancellation, $V_1 - V_b$ and $V_2 - V_b$ will not only be exact mirror patterns but will also be in the ratio $(V_1 - V_b)/(V_2 - V_b) = m/(m - 1)$. In exactly the same fashion it may also be seen that $V_3 - V_a$ and $V_4 - V_a$ are exact mirror patterns under cancellation conditions and that

$$(V_3 - V_a)/(V_4 - V_a) = n/(n - 1).$$

Thus, in searching for cancellation, the mirror image property may be utilized, and when cancellation is obtained the amplitudes of the measured electrode potentials with respect to the potentiometer junctions may be compared for consistency with the potentiometer settings.

If electrode positions 1, 2, 4 and G are fixed, and if the 1-2 potentiometer setting is fixed, a search for cancellation may be undertaken with the two remaining variables; electrode 3 location and the setting n of the 3-4 potentiometer. The search process can be visualized very clearly in figure 7. The image surface of a typical homogeneous torso[10] may be used fruitfully as a guide in selecting points and potentiometer settings for which cancellation may be expected.

The geometric interpretation of cancellation presented here is an exceedingly helpful viewpoint which gives insight into the three-dimensional nature of the cancellation search conditions, the way in which the variables enter into the experiment and the significance of the potentiometer settings. It is also helpful in the interpretation of the behavior of the four-electrode system; for example, in understanding why some cancellations are more sharply defined than others. A knowledge of the dipole component behavior of the subject under test is also helpful. However, despite its usefulness as an aid for procedures and reasoning, the geometric interpretation in terms of vectors is not an essential aspect of the theory since the entire matter may be expressed in terms of algebraic equations of the type given in equation (1).

It may be seen from the theory which has been presented that the existence of cancellation depends in no way upon the location in image space of the coincident points a and b with respect to the dipole mid-potential point 0, contrary to the claims of Schmitt and associates.[3] This is also emphasized in appendix III where the preamplifier common-mode rejection characteristics are seen to be related to this independence of 0. It may also be seen that the medium shape and inhomogeneities do not prohibit the attainment of cancellation since the theory applies for any medium shape and for an inhomogeneous medium. In addition, if the location of the dipole moves with time, it is obvious that complete

* Anatomic points within the body generally have higher potentials than body surface points. Thus, by definition of the fixed unipolar vectors, it may be seen that those associated with interior anatomic points are larger and lie further away from 0 in image space.[12] Hence, the loci of both the points a and b lie outside the medium but inside the image surface.

cancellation cannot occur for then the formerly fixed unipolar vectors become variable; consequently, $\mathbf{c}_a$ and $\mathbf{c}_b$ would vary differently with time and prevent $V_a - V_b$ from being zero during the heart complex under study.

Appendix II

Cancellation Coefficient

As a result of a variety of factors previously mentioned, the minimum potential difference between the potentiometer taps a and b, $V_a - V_b$, when the best cancellation is obtained experimentally will generally be small but not exactly zero. Hence, it is desirable to define a quantity which is a meaningful measure of the degree of cancellation, and which also can be interpreted as a measure of the nondipolar content of the potentials being measured.

An approach to a suitable definition may be found by first referring to a bridge circuit simpler than the four-electrode system; namely, the Wheatstone bridge of figure 8. The degree of cancellation in such a bridge, more commonly called the bridge null, is defined by the quantity $2r/E$ where r is the residual (or null) voltage equal to the magnitude of the potential difference $V_a - V_b$ and E is the magnitude of the potential difference applied to the bridge. The factor of 2 used in this definition arises from the desire to define a quantity having an average maximum possible value equal to 1.0. Thus, for a given setting of tap a with b considered variable, extreme values of the magnitude of $V_a - V_b$ are mE when $n = 0$ and $(1 - m)E$ when $n = 1$, the average magnitude being $E/2$. Hence, for random initial settings of tap a, the worse possible null will be, on the average, $2(E/2)/E = 1.0$.

Turning to the equivalent bridge circuit[14] of figure 1, also shown in figure 8, it may be seen that the potential difference between points 1 and 2 is not necessarily the same as that between points 3 and 4, which differs from the case of the Wheatstone bridge. It is plausible to extend the Wheatstone bridge definition to this case by using the average magnitude of the potential differences $V_1 - V_2$ and $V_3 - V_4$ in place of E. Hence, the cancellation coefficient c given in figure 8 is seen to be a natural outgrowth of a definition used in a simpler case. The residual voltage r and the magnitudes of $V_1 - V_2$ and $V_3 - V_4$ are directly measurable quantities; and hence c may be calculated directly from raw data. As an illustrative example, consider the peak-to-peak potentials illustrated in figure 2; $V_3 - V_4 = 3.6$ mv and $r = 0.05$ mv. Also, $V_1 - V_2$ (not shown) was in this case equal to 2.9 mv. Therefore,

$$c = 2\,\frac{0.05}{\dfrac{2.9 + 3.6}{2}} = 0.031$$

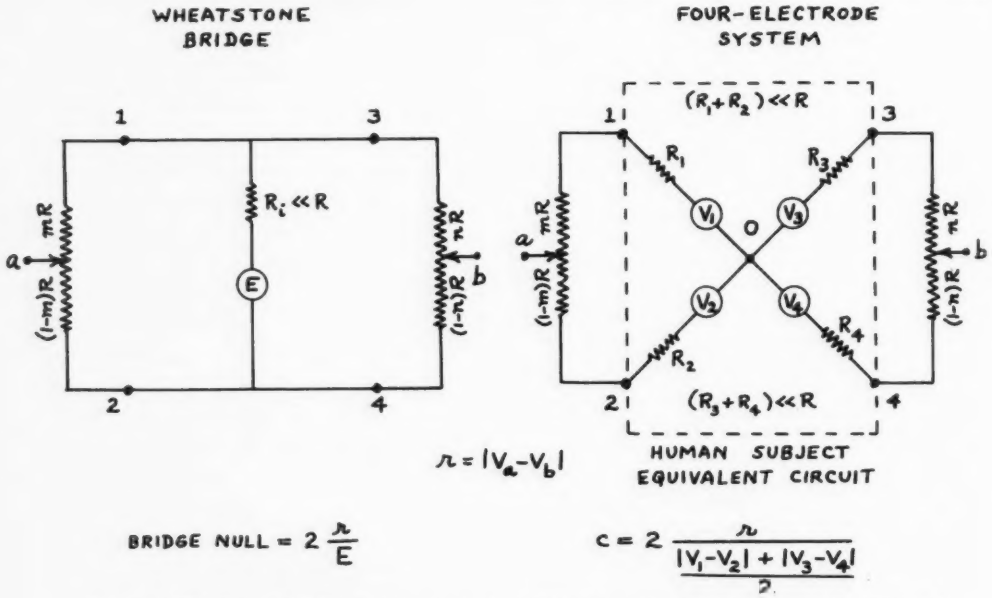

Fig. 8. A Wheatstone bridge and the equivalent bridge circuit of the four-electrode system of figure 1 are compared for the purpose of defining the cancellation coefficient c which is a quantitative measure of the nondipolar content of body-surface potentials. In both cases the internal generator resistance is assumed to be negligible in comparison with the potentiometer resistance, R.

The definition of cancellation coefficient employed by Schmitt[3] is different from the type given here. When the method of definition presented here is applied to Schmitt's system, assuming that the Wilson central terminal is perfect, the cancellation coefficients calculated will be slightly smaller than Schmitt's coefficients. For potentiometer settings near the mid-position the coefficients agree exactly, but for settings over the range $\frac{1}{3}$ to $\frac{2}{3}$ the coefficients calculated by the definition presented here are as much as 15 per cent lower than Schmitt's; that is, Schmitt's coefficient of 0.05 would be calculated as 0.04, in an extreme case. For all practical purposes, however, results calculated from either definition may be compared directly.

The cancellation coefficient defined in figure 8 may be regarded as a measure of the approximate average non-dipolar content of the potentials at electrodes 1, 2, 3 and 4. To show the basis for this it is necessary to formulate a theoretical expression for $V_a - V_b$, which can only be done approximately when conditions are not ideal. One approach is to regard each of the unipolar voltages V_1, V_2, V_3 and V_4 as consisting of a dipolar portion plus a small nondipolar component, and to assume that the residual arises solely from the nondipolar portion which is a conservative basis since other effects also contribute to the residual. For simplicity of illustration, suppose the nondipolar portion is proportional to the magnitude of the unipolar voltage. This of course is not necessarily exactly true, but it will serve to show the way in which c can be a measure of the nondipolar portion. It was shown in appendix I that $V_a = V_1(1 - m) + mV_2$ and in similar fashion it follows that $V_b = V_3(1 - n) + nV_4$. Now if the unipolar voltages are expressed as $V_n = V_{dn}(1 \pm \delta)$ where $n = 1, 2, 3, 4$ and δ is the nondipolar fraction of V_n, then $V_a - V_b$ may be written as

$$V_a - V_b = V_{d1}(1 - m) + mV_{d2} - [V_{d3}(1 - n) + nV_{d4}] + r$$

where the sum of all terms except r represent the cancelling portion of $V_a - V_b$ and is zero. It is reasonable to express the noncancelling portion of $V_a - V_b$ as the root-mean-square of the nondipolar portions, in which case the residual voltage is given approximately by

$$r \doteq [V_{d1}^2\delta^2(1 - m)^2 + V_{d2}^2\delta^2m^2 + V_{d3}^2\delta^2(1 - n)^2 + V_{d4}^2\delta^2n^2]^{\frac{1}{2}}$$

Since the dipole contributions to the unipolar voltages usually constitute over 90 per cent of the total, it is a good conservative approximation to use the total unipolar voltages in this expression for r; thus,

$$r \doteq \delta[V_1^2(1 - m)^2 + V_2^2m^2 + V_3^2(1 - n)^2 + V_4^2n^2]^{\frac{1}{2}}$$

Hence, a theoretic expression for the cancellation coefficient in terms of the nondipolar fraction δ of the unipolar voltages is

$$c \doteq \delta \frac{\frac{1}{4}[V_1^2(1 - m)^2 + V_2^2m^2 + V_3^2(1 - n)^2 + V_4^2n^2]^{\frac{1}{2}}}{|V_1 - V_2| + |V_3 - V_4|}$$

For the ranges of voltages and potentiometer settings encountered in practice this last expression is very nearly equal to δ; and hence the cancellation coefficient is interpretable as an approximate measure of the fractional nondipolar voltage. As a numerical illustration, suppose $V_1 = -V_2 = V$ and $V_3 = -2V_4 = 2V$ and $m = \frac{1}{2}$. Then n may be calculated approximately from $V_1(1 - m) + mV_2 = V_3(1 - n) + nV_4$, whence $n = \frac{2}{3}$. Substituting into the equation for c results in $c = 0.94\delta$ for this case. Other examples may be applied with similar results. For instance, with $V_1 = -V_2 = V$, $V_3 = -V_4 = 2V$ and $m = \frac{1}{4}$, n is calculated to be $\frac{3}{8}$ and the calculated value of c is 1.1δ.

If the nondipolar content is not assumed proportional to the magnitude of the unipolar potential, the quantitative interpretation of c becomes modified somewhat. For an *extreme* illustration, suppose in the last numerical example that V_1 only contains nondipolar potentials and that V_2, V_3 and V_4 are perfectly dipolar. Placing these last three potentials equal to zero in the numerator of the expression for c results in $c = \delta/2$. Thus, c indicates one half the nondipolar content of V_1 in this case. Although c tends to be a somewhat optimistic measure of dipole action in this instance, it should be noted that c is still twice the average, $\delta/4$.

Appendix III

Cancellation Preamplifier

The residual voltage $r = V_a - V_b$ is ordinarily too small to be measured accurately by a standard electrocardiograph, as illustrated in figure 2, usually being in the vicinity of 50 microvolts peak-to-peak. However, a battery-operated preamplifier with good common-mode rejection characteristics may be constructed from parts costing about $90 (the two micropots cost about $50) which not only provides the requisite additional amplification (about 15 times in voltage) but also contains other provisions such as a special lead selector switch and a 0.2 mv. standardization pulse which makes it convenient for the pursuit of cancellations on the human subject. The preamplifier is connected ahead of a standard single-channel electrocardiograph such as a Sanborn Viso Cardiette and when used in this manner enables the cancellation search to be carried out conveniently since the residual voltage can be recorded and studied immediately. A complete schematic of a suitable preamplifier is given in figure 9.

Power Switch. In the OFF position, filament (A) and plate (B) supply batteries are disconnected from

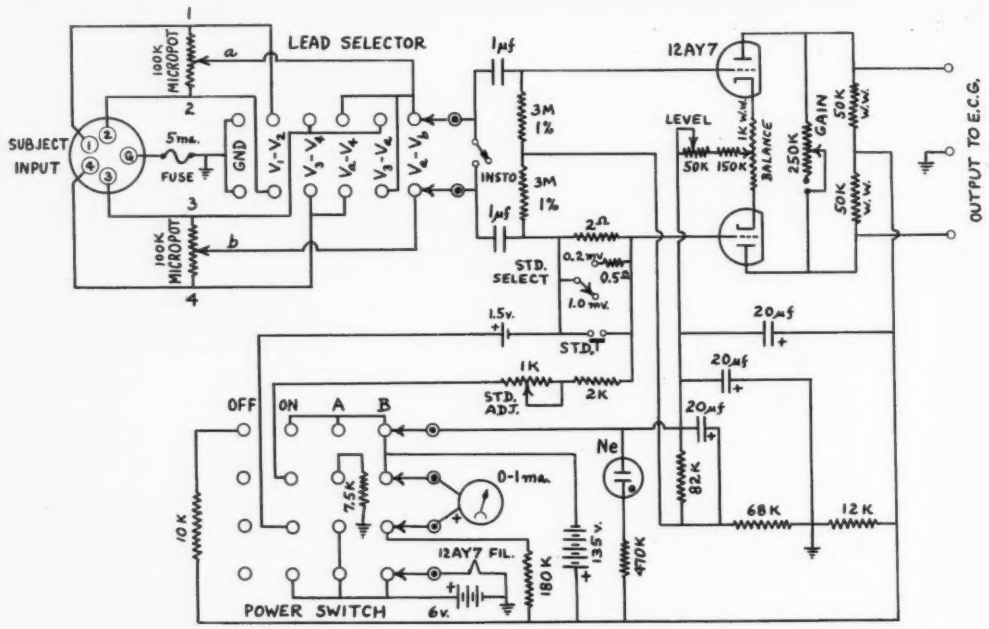

FIG. 9. Complete schematic of one-tube cancellation preamplifier useful in the system of figure 1 for performing cancellation experiments on the human subject using a single-channel electrocardiograph.

the circuit and the neon tube pilot circuit is shunted by a 10K resistor for rapid extinction. In the ON position, both A and B supplies are connected and the 0-1 ma. meter is inserted in the standardization circuit. The meter reading may be adjusted to 0.5 ma. by the 1K STD.ADJ. control, in which case the standardizing pulse in series with the 12AY7 grid is either 1.0 mv. or 0.2 mv. depending upon the position of the STD.SELECT switch. In the A and B positions of the POWER SWITCH the meter is switched so as to check the 6-volt filament battery and the 135-volt plate battery, respectively, the 7.5K and 180K resistors serving to convert the milliammeter to a voltmeter. In normal use the POWER SWITCH is in the ON position.

Lead Selector. In the GND position of the LEAD SELECTOR switch, the preamplifier input is grounded. In the next two positions $V_1 - V_2$ and $V_3 - V_4$ are presented to the preamplifier; their peak-to-peak values are used in calculating the cancellation coefficient. Following the method of cancellation search discussed previously, selector positions $V_a - V_4$ and $V_3 - V_a$ may be examined in the next two positions for mirror patterns. For convenience, the $V_a - V_4$ polarity is automatically reversed in the switching circuit so that patterns identical in shape are observed when the mirror condition is satisfied. In the final position of the LEAD SELECTOR switch the residual voltage $V_a - V_b$ is connected to the preamplifier input. Two 10-turn, 100K, 0.1 per cent linearity micropots are contained in the preamplifier and are automatically connected across leads pairs 1-2 and 3-4. A 5-ma. fuse protects the subject.

Preamplifier. The preamplifier is a differential amplifier direct-coupled to the electrocardiograph. The high ratio of cathode return to plate load enables considerably more common-mode rejection than found in commercial electrocardiographs; this is necessary to minimize 60 cycles per second interference at the higher amplification provided. The low-frequency response of the preamplifier is down 3 decibels at 0.05 cycles per second, while the high-frequency response is constant to at least several thousand cycles per second. The overall high-frequency response is limited by the electrocardiograph, in particular the galvanometer, which in a Sanborn Viso Cardiette is down 3 decibels at about 60 cycles per second. The 1K BALANCE control is used to equalize the output plate-to-ground voltages, while the 50K LEVEL control is used to set the direct potential of the output. This should be set for ground potential with the GAIN control set at maximum. The BALANCE adjustment is far more critical than the LEVEL, but remains stable over a period of several hours provided the batteries are stable and the 12AY7 is a selected low-noise tube. The BALANCE and LEVEL adjustments may be made with a direct current vacuum-tube voltmeter connected from outputs to

ground. The operating point of the 12AY7 may be changed if desired by altering the 68K resistor with little influence on the output level. In normal operation the electrocardiograph gain control should be permanently set to its maximum value and the 250K preamplifier GAIN control should be used to set the recording level. This procedure is essential in order to avoid amplitude limiting in the electrocardiograph when signals other than $V_a - V_b$ are being measured. With the LEAD SELECTOR in the GND position and the preamplifier GAIN at maximum, the 0.2 mv. STD. pulse should cover the full width of the recording paper and the baseline should be stable and show only about 5 microvolts of noise.

Micropots. The choice of 100K for the micropots is an optimum value bordered on both sides by two conflicting requirements. On one hand, the micropots must have a resistance large compared with the electrode resistance, which is not negligible when small electrodes are used. On the other hand, the micropots must have a resistance small compared with the preamplifier input resistance in order to minimize 60 cycles per second interference and ground signal unbalance. The impedance of several different types of electrodes was measured with the help of Dr. Herman P. Schwan with the following results: Standard electrocardiograph electrodes (1½ inches × 2 inches) display very small polarization impedance when the skin is rubbed thoroughly, approximately 30 ohms. Circular disc nickel electrodes (½ inch diameter) display a polarization impedance comparable to that of 27 gage hypodermic needles, about 1500 to 2000 ohms. The ratio of resistance to reactance is about 0.4 at frequencies from 10 to 1000 cycles per second. Thus, it may be seen that the use of 100K micropots leads to errors of less than 2 per cent with these electrodes. The use of 3 megohm resistors in the preamplifier is slightly higher than in conventional design with the result that there are small grid-current effects, which however are not serious. It is necessary to use these large values to minimize 60 cycles per second and ground-signal feed through when the residual is being measured. Suppose the right leg ground-signal voltage with respect to the micropot taps is about 2 mv. and that the micropots are set to the worse possible condition; i.e., one micropot set to zero or maximum and the other micropot set to mid-position. Then there is, in effect, a 50K unbalance in the series resistance feeding the preamplifier. Therefore, one preamplifier grid will receive the 2 mv. ground signal while the other grid will receive 3000/3050 times 2 mv. or 1.97 mv. Thus, there will be a 30 microvolt ground-signal residual under these extreme conditions, even though the potentials of electrodes 1, 2, 3, and 4 cancel perfectly. A typical maximum feed through is about 10 microvolts in practice, and is usually small compared with the residual from the noncancelling portion of the other signals. It is informative to note that excellent cancellations are obtained, as expected theoretically, even though measurements are made with respect to the grounded right leg, and this would also be so for other ground points. This gives further evidence that cancellation existence does not depend upon achieving a reference potential which coincides with the electrical center of the heart.

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The Effects of Repetitive Electric Cardiac Stimulation in Dogs With Normal Hearts, Complete Heart Block and Experimental Cardiac Arrest

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Direct cardiac stimulation was conducted in the open chest. In normal animals, auricular stimulation at frequencies faster than the spontaneous rate caused little change in vascular pressures or cardiac output. Comparable ventricular stimulation in the same animals caused falls in cardiac output and blood pressure, with elevations in venous pressure. In contrast, ventricular stimulation in animals with complete heart block caused elevations in cardiac output and blood pressure, and declines in venous pressure. A study was also made of repetitive stimulation in experimental cardiac arrest. Occasionally pacemaking was of value in the resuscitation, but in most cases effective contractions could not be induced with stimulation.

REPETITIVE electric stimulation of the animal heart for investigative purposes has been standard laboratory procedure for many decades. The interest of clinicians has been sporadically directed to electric pacemaking as a tool in the treatment of clinical cardiac arrest since it could be, in theory, a means of dealing with this disastrous situation by meeting a specific need with a specific therapeutic provision. Several reports are available, concerned with the evaluation of pacemaker cardiac resuscitation under various conditions, in experimental animals[3-7] and in man.[1, 2]

With increasing interest in this form of therapy, it becomes desirable to obtain a more precise understanding of the potentialities and limitations of cardiac stimulation, as well as a more definitive understanding of the type of arrest in which its use will give a reasonable hope of beneficial effect. The present study was undertaken with these objectives. During the performance of the experiments, data were obtained which may have wider application relevant to some of the physiological mechanisms involved in serial auricular and ventricular extrasystoles.

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General Methods

Sixty-six mongrel dogs were used, ranging in weight from 7 to 20 Kg, and satisfactory technical conditions were realized in 51 experiments. Twenty-three to 30 mg. of Nembutal per kilogram were given intravenously, tracheostomy was performed, and the animal placed on a positive pressure respirator (supplied with 100 per cent oxygen in experiments where cardiac outputs were measured). Cardiac stimulation was usually conducted through a left thoracotomy in the fifth intercostal space. In experiments requiring an auriculoventricular block, this procedure was done through a right thoracotomy in the fourth intercostal space,[8] the incision was closed with water seal drainage, and at least an hour was allowed to pass before reopening the chest for pacemaking.

In cases where it was desirable, cardiac output was obtained by the dye dilution method of Steward[9] and Hamilton.[10, 11] A repeatedly calibrated photometer was employed which continuously measured the dye concentration of flowing arterial blood.[12] Standard limb electrocardiogram, blue-dye cardiac output, and arterial and venous pressures were recorded on a multichannel direct writing oscillograph. Vascular pressures were detected with inductance type transducers, the natural frequency of the measuring and recording systems being greater than 30 cycles per second, when tested by recording pressure within a balloon during explosion.

Bipolar concentric electrodes were used for stimulation. These consisted of an insulated stainless steel syringe tubing, which contained an insulated stainless steel wire, the enamel at the tips of both components being filed off. Polar distance was 1 to 3 mm., and electrode resistance in position in the heart was 5000 to 8000 ohms. Current source was a Goodwin condensor stimulator. Three to 5 volts were routinely used, with a 1 millisecond falling phase. The stimulating electrode was placed in position like a dart so that both poles were in the myocardium.

Blood loss from surgical procedures, or tests, was replaced with plasma expander or whole blood, as soon as possible after the exact moment of loss. Specific details of methods of creating arrest, or alterations in the above technique, are given under the appropriate section.

Results

Repetitive Auricular and Ventricular Stimulation in Animals with an Intact Conduction System. Stimulation was conducted in seven animals. Cardiac output, electrocardiogram, arterial blood pressure, and, in most cases, femoral venous pressure were studied. Stimulation was at 10 to 70 impulses per minute faster than the prevailing spontaneous rate. It was not possible to drive the heart slower than the spontaneous beat. Records were obtained first with the spontaneous rhythm, then with ventricular stimulation at different locations, then with auricular stimulation, and finally after cessation of stimulation. In any given series (fig. 1 A, B) auricular and ventricular pacemaking was conducted at the same rate. The entire sequence was usually performed in 8 to 10 minutes. In no case did the stimulation produce ventricular fibrillation.

Repetitive stimulation of the auricles, irrespective of site, produced a total picture comparable to that occurring with sinus control, but at a faster rate. The electrocardiogram was easily controlled, with cessation of spontaneously occurring P waves, and unchanged QRS complexes. The pulse was regular, and mean blood pressure was maintained with a slight fall in pulse pressure (fig. 1 A_5, B_5). The configuration of the venous pressure was usually unchanged (fig. 1 A_5, B_5). The cardiac output (fig. 2) usually remained essentially unchanged, with a consequent reduction in stroke volume.

In contrast to the minor changes induced by auricular driving, repetitive ventricular stimulation precipitated marked alterations in cardiocirculatory function. Electrical events of the cardiogram could rarely be totally controlled. In the majority of cases P waves continued to appear (fig. 1 C, D, E), often at their original rate (C, E). The difficulty, in the normal animal, of completely dominating auricular rhythm by retrograde conduction from the ventricle has been recognized before.[13, 14] The form of the artificially produced QRS complexes depended upon the site of stimulation, and was in conformity with known rules of electrocardiographic localization.[15] However, details of QRS duration, amplitude, and timing were subject to considerable variation, a variation which often was obviously related to the independently continuing rhythm. Thus in figure 1C, in which four P waves corresponded to every five driven ventricular beats, shifts in the duration, amplitude, and time of onset of the QRS complexes occurred in cycles of four with resultant inconstancy of the period of diastolic filling. That this electrical shift related to the effectiveness of the individual myocardial contractions is evident from the record of the simultaneous arterial pressure (fig. 1C), in which the strength of the pulses also varied in cycles of four beats. In the case shown, the strongest mechanical beats occurred, after the periods of longest diastole, when the ventricular stimulus came just after the P wave (indicated with arrows in the figure). The weakest pulses were found when the ventricular stimulus was delivered after the shortest diastole (fig. 1C), approximately where the auricular driven QRS would have occurred. In all cases in which analyzable auricular interference of this sort was encountered, the decisive factor in determining the strength of the beat was not the source of excitation, whether it be spontaneous auricular or artificial ventricular. Of critical importance, however, was the element of timing in ventricular excitation as it related to the duration of diastole.

During ventricular stimulation, marked changes were detected in vascular pressures. Large falls in blood pressure were recorded,

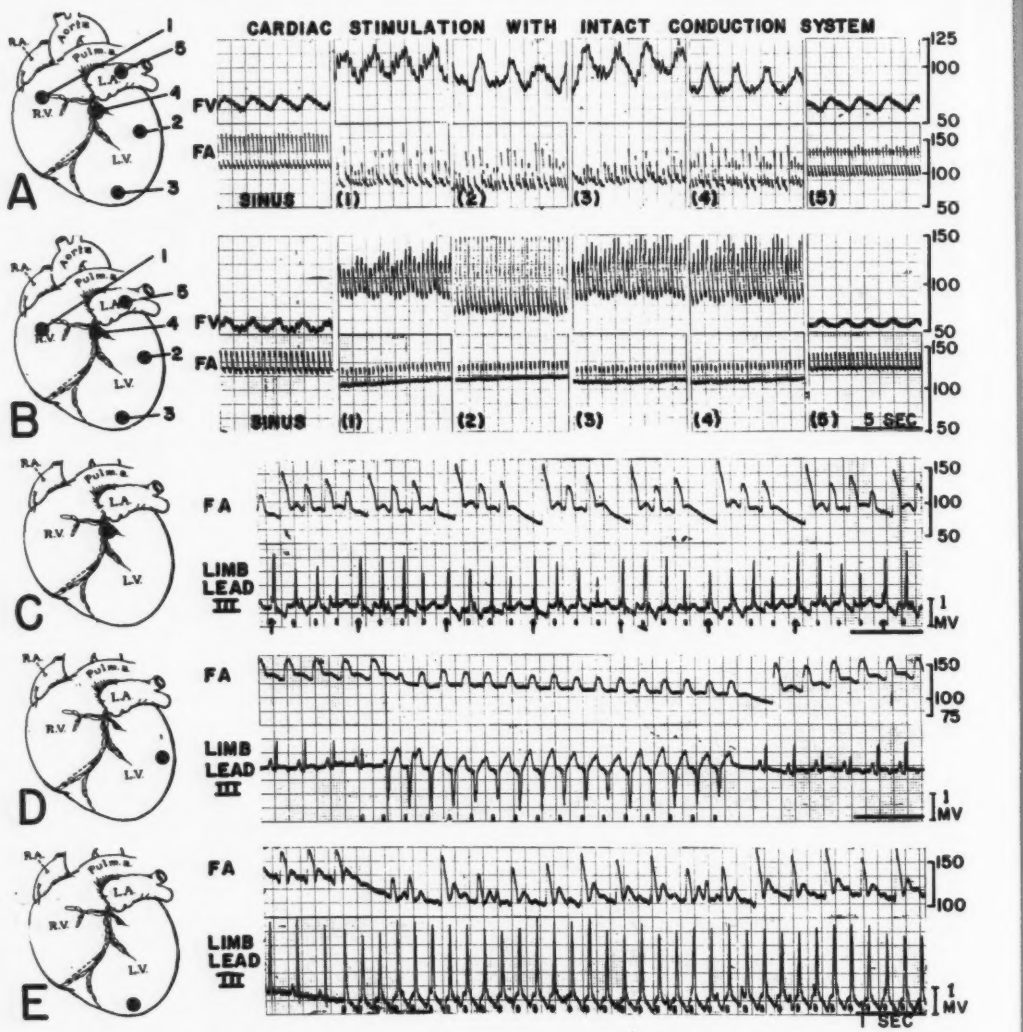

FIG. 1. Repetitive stimulation of intact heart with 3 to 5 volts. Stimulation sites are indicated by black circles on the insets. Femoral venous (FV) and arterial (FA) calibrations are in millimeters water and mercury respectively.

A. Ventricular (1–4) and left atrial (5) stimulation at 240 per minute. Sinus rate (at left) was 185. Note similarity of effect on venous and arterial pressures irrespective of the ventricular stimulation site.

B. Variation of the effects noted in A. Sinus rate was 160, and stimulation at 190 per minute.

C. Alteration of ventricular driving pattern, by persistance of active sinus mechanism. Sinus rate was 154 and stimulation 190 per minute.

D. More complete control with ventricular stimulation. Sinus rate was 148 and stimulation 190 per minute.

E. Alternating pulse obtained with 240 per minute stimulation. Sinus rate was 150 per minute.

irrespective of whether the driven pulse was regular (fig. 1B) or irregular (fig. 1A), the latter being more common. Moderate or marked elevations in venous pressure were found (fig. 1 A, B), often with the development of bizarre huge venous pulses with each electrically driven beat (fig. 1B).

Ventricular driving with an intact conduc-

ion system caused a reduction in the cardiac output and stroke volume which ranged from a small decline to a precipitous drop (fig. 2).

The foregoing data indicates that repetitive auricular stimulation in normal animals exerts a basically different influence on cardiac function than comparable ventricular stimulation. Pacemaking of any portion of the auricles caused minor alterations of function which were explicable solely in terms of change of rate. Comparable ventricular stimulation at different sites uniformly produced injurious changes, with incomplete control of electrocardiographic pattern, irregular pulse, decline of blood pressure, rise in venous pressure, and fall in cardiac output and stroke volume. It is thought that the difference is due chiefly to double ventricular excitation during ventricular pacemaking, through the normal auriculoventricular pathways and from the ventricular stimulation site.

Repetitive Ventricular Stimulation in Animals with Acute Complete Heart Block. In animals with acute complete heart block the occurrence, during stimulation, of dual excitation of the ventricles from competing auricular and ventricular sources is eliminated. Repetitive ventricular stimulation was carried out in seven animals in which a complete heart block had been established 60 to 90 minutes previously. Rates in this group ranged from 24 to 45 per minute. It was not possible to drive the heart at a rate slower than the spontaneous rhythm. Auricular pacemaking was of course without effect on the ventricular pattern. After studies were obtained at the idioventricular rate, ventricular stimulation was performed at various frequencies and this was followed by a final control study at the cessation of stimulation. There were no instances of ventricular fibrillation precipitated by the electrical pacemaking.

In a given animal, stimulation at different points on both ventricles yielded similar results except for the predictable differences in the electrocardiogram (fig. 3). With the onset of pacemaking, electrical events of the ventricle were instantly and easily brought under complete control, the driven QRS complexes being uniform in appearance and timing with no tendency for spontaneous ventricular discharges (fig. 3). The ventricles relinquished their automaticity to such an extent that, after cessation of stimulation, it often required many seconds before the ventricles again took up their original spontaneous rate (fig. 3D). During ventricular stimulation, the P waves continued at their original rate (fig. 3), indicating absence of retrograde conduction.

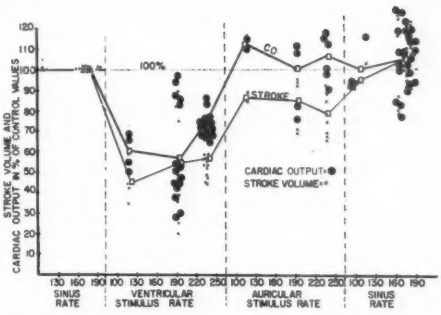

FIG. 2. The effect of left auricular and ventricular repetitive stimulation upon cardiac output and stroke volume in intact heart, expressed as changed from the initial sinus values. Ventricular driving in a given animal yielded similar results irrespective of stimulation site.

In contrast to the irregular arterial pulse often produced by ventricular stimulation in the intact animal, regular pulses could be driven to the rate of 190 and frequently to 240 per minute (fig. 3 A–D). In general, the systolic blood pressure remained at about the same level as before, with marked elevation of the diastolic and mean pressures (fig. 3 A–C), the optimal mean blood pressure generally being with stimulation at 144 per minute. When starting with very slow spontaneous rates, however, both systolic and diastolic pressures were increased (fig. 3D), by ventricular pacemaking at faster rates.

Venous pressure regularly declined until the stimulus frequency of 190 per minute was exceeded, beyond which it rose again (fig. 3 C, D). Similar central venous pressure falls were recorded from the right auricle in two animals.

It has been shown[16] under conditions similar to those prevailing in the present study, that cardiac output is diminished in animals with heart block because of a reduction in rate so extreme that a complete stroke volume adjustment is not possible. In the presence of

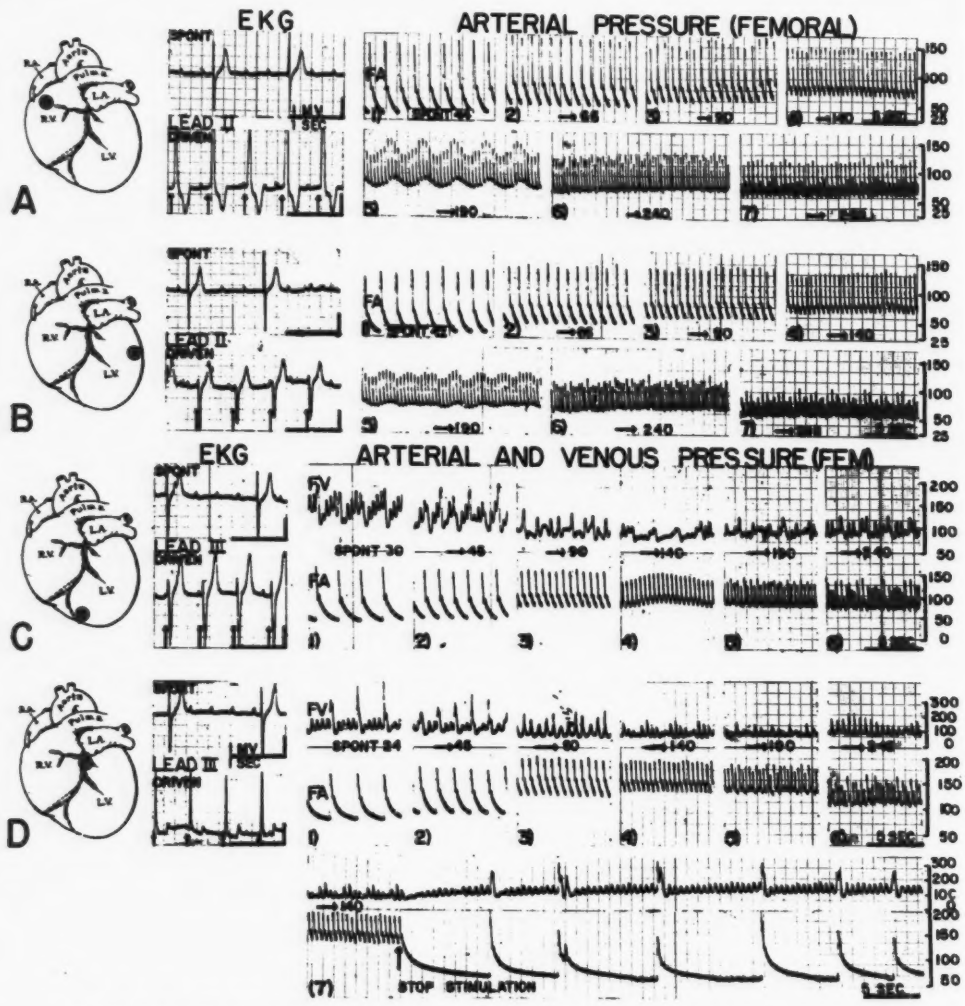

FIG. 3. Effect of stimulation at varying rates and at different ventricular sites in animals with complete heart block. In each case locus of stimulation is marked in the inset, spontaneous and driven electrocardiograms shown on the left, and arterial pressure (FA) recordings on the right. Femoral venous (FV) records are also included in C–D. Note marked slowing of pulse rate at cessation of stimulation in D. Arterial and venous calibrations are in mm mercury and water respectively. Voltages were 3 to 5.

such a low output due to bradycardia, ventricular stimulation at faster frequencies increased the cardiac output (fig. 4). The output gains were most striking when the spontaneous rates were slowest. Starting with idioventricular rates of 24 to 27 per minute, the cardiac output was increased an average of almost 400 per cent with ventricular pacemaking at faster rates. With initial rates of 30 to 33 per minute the gain in output was more than 200 per cent. With initial rates of 42 to 45 per minute, the output rose 100 per cent. Although the pre-existing idioventricular rate determined the magnitude of gain, the pattern of cardiac output rise was the same starting with all rates from 24 to 45 per minute. Almost all the out-

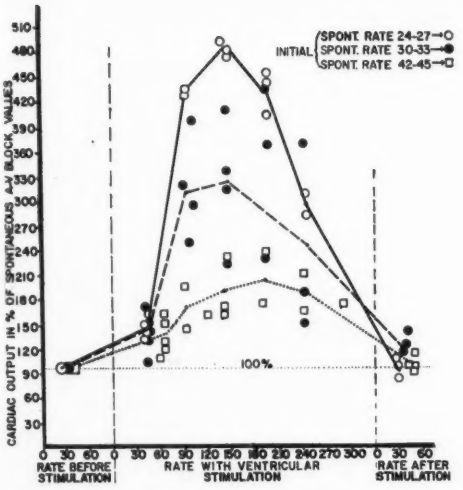

FIG. 4. Effect of ventricular stimulation at different rates on cardiac output of dogs with acute complete heart block, expressed in per cent of initial spontaneous idioventricular value. Note how the spontaneous rate determined the magnitude of increase.

put augmentation occurred by the time the stimulus frequency reached 90 per minute, with an additional small rise to the stimulus frequency of 144 or 190 per minute (fig. 4). Further increments in stimulus rates caused declines in the cardiac output.

The mechanism of the beneficial effect of ventricular pacemaking on the cardiac output in these cases is evident from fig. 5. There is a definite tendency, as the rate is artificially increased by stimulation, for the stroke volume to remain fixed until the rate of 90 is attained, above which the stroke volume progressively diminishes. Accordingly, cardiac output rises linearly with the rate up to a stimulus frequency of 90 per minute.

In summary, the cardiovascular status of dogs with acute heart block is brought by ventricular driving from a low to a higher level of effective function, as judged by measures of vascular pressures and cardiac output. In contrast to ventricular pacemaking in animals with an intact conduction system, the rate and electrocardiographic patterns are easily controlled and regular arterial pulses are induced to frequencies of 190 to 240 per minute.

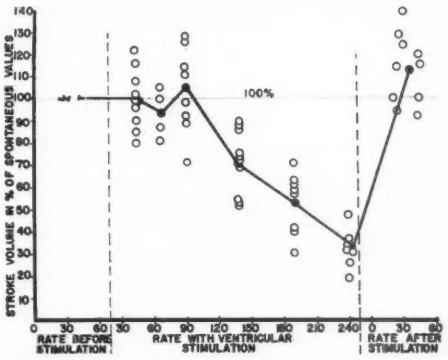

FIG. 5. Effect of ventricular stimulation at different rates on stroke volume of dogs with acute complete heart block, expressed in per cent of initial spontaneous value. Note tendency of stroke to be fixed up to the rate of 90 per minute.

Repetitive Ventricular Stimulation in Animals with Acute Complete Heart Block in Shock. A controlled shock state was established in three dogs with acute heart block by permitting the animals to bleed from an arterial cannula into a reservoir suspended at a height calculated to give the desired blood pressure. Fifteen to 30 minutes were allowed for equilibration. Experiments were done with systolic pressure levels of 90, 60, and 30 mm. Hg. Idioventricular rates in these cases were 30, 39, and 21 per minute with cardiac outputs of 50, 40, and 20 cc per kilogram, respectively. In the first two cases stimulation at faster rates did not affect the greatly reduced cardiac output, and in the last case caused a 30 per cent fall.

Repetitive Ventricular Stimulation in Animals with Experimental Cardiac Arrest. Cardiac arrest, with absent recordable pulse, or with a heart rate of less than 10 per minute, was created 45 times in 34 animals. Thoracotomy had been previously performed. Stimulation was accomplished as described elsewhere in this study. In all the cases included in this report in which electrical pacemaking was tested, stimulation was started in the absence of ventricular fibrillation. Because of the poor condition of the heart, fibrillation frequently began spontaneously, with stimulation or with minimal handling of the heart. It was our impression that fibrillation was somewhat less

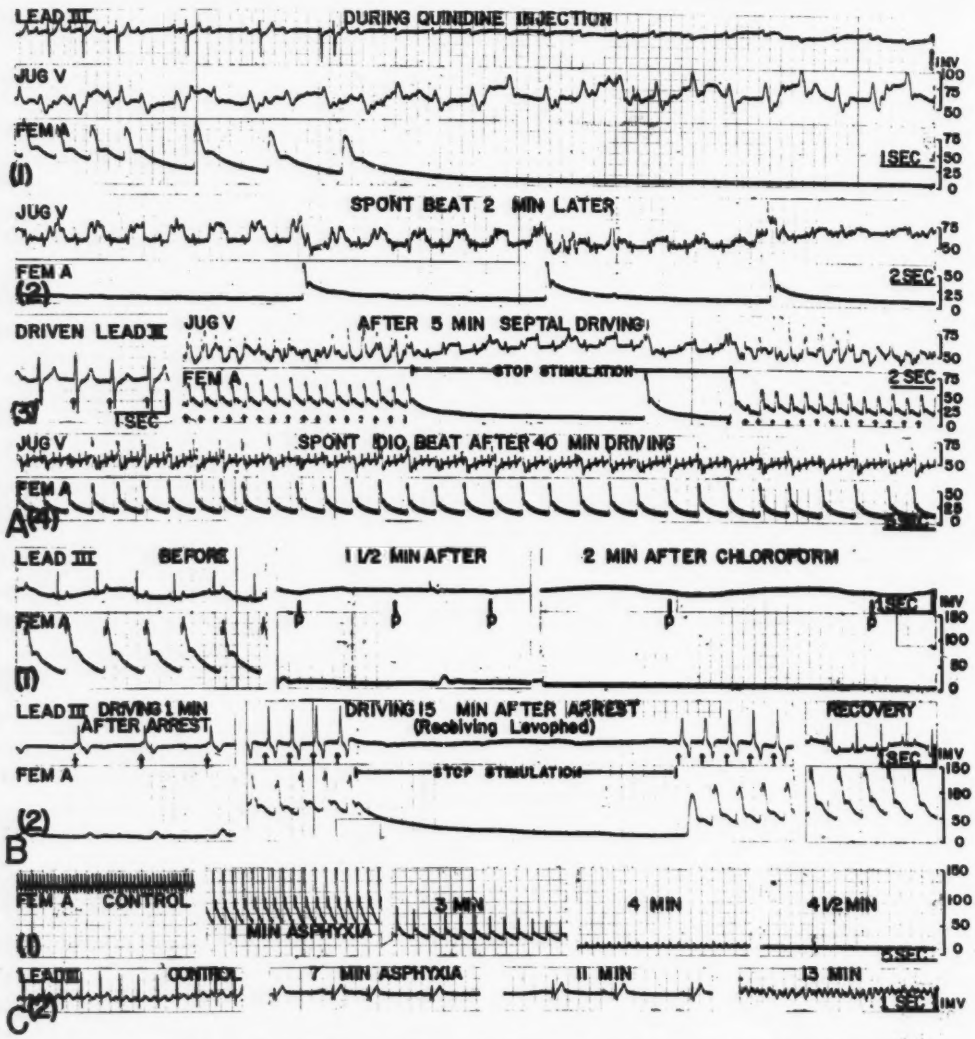

FIG. 6. Experimental cardiac arrest. Electrocardiogram, jugular venous (Jug V) and/or femoral arterial (Fem A) pressures are included and calibrated in millimeters water or mercury respectively.

A. Animal had received 21 mg per kilogram 15 minutes before with consequent hypotension. Additional 21 mg per kilogram injected as indicated. Ventricular driving at 90 per minute, 5 volts.

B. Arrest with endotracheal chloroform. Ventricular driving at 5 volts, 50 or 140 per minute.

C. Arrest with asphyxia, showing persistance of sinus driven electrocardiogram (2) long after blood pressure was not recordable (1).

likely to be precipitated by stimulation than by massage.

Acute asphyxia, accomplished by clamping the endotracheal tube, was used to produce arrest 12 times in 8 animals under light Nembutal anesthesia. After the animals had been pulseless for at least two minutes, they were placed back on the respirator, and stimulation was started. The pattern of arrest in general followed that illustrated in figure 6C. In the example shown, effective myocardial contractions, as evidenced by absence of recordable

arterial pulses, were abolished after four and one half minutes of asphyxia. With inspection of the heart, contractions were virtually indiscernible. Sinus driven QRS complexes, however, continued for eight more minutes until the animal fibrillated after 13 minutes of acute anoxia (fig. 6C). In none of these animals was there electrocardiographic evidence of an absolute conduction failure until fibrillation began terminally. Repetitive ventricular stimulation, before the onset of fibrillation, did not alter the existing course in a single case. After stimulation had failed, the application of massage, appropriate drug therapy, and defibrillation (when necessary) was successful in reviving the animals in 6 of the 12 arrests.

Using chloroform inhalation, or chloroform with basal Nembutal anesthesia, 20 arrests were produced in 14 animals. After the animals had been pulseless for at least two minutes, the respirator was changed to air and stimulation started. In 17 cases, the type of arrest was similar to that described with asphyxia, with electrocardiographic evidence of a functional conduction mechanism long after the blood pressure had approached 0. Ventricular pacemaking did not alter the course in any of these instances. In 9 of the 17 arrests, massage was instituted after stimulation had failed, and recovery accomplished five times. The remaining three arrests were of a different type, and were characterized by a sudden unexpected complete heart block and ventricular asystole immediately after a time when arterial pulses were still present (fig. 6B). P waves continued, but there was no electrocardiographic indication of ventricular activity. In this state, ventricular contractions could be induced by mechanically stimulating the ventricle with the tip of the finger. Ventricular pacemaking in these three cases induced contractions of approximately the same vigor as had been present just before the standstill, as gauged from the arterial pulse (fig. 6B). Pacemaking alone did not, however, ensure recovery, for although contractions were being initiated, they were feeble, as gauged from the low blood pressure (B-2). The use of diluted intravenous levarterenol bitartrate, in addition to stimulation, resulted in the restoration of a normal blood pressure (B-2) in all three instances. During the maintenance of beats with ventricular pacemaking, the stimulator was turned off at intervals. When complete heart block with ventricular asystole persisted during these test periods (B-2), P waves were the only electrical activity in the electrocardiogram, and arterial pulses promptly ceased. In these three dogs, it was necessary to maintain the cardiac rhythm with the pacemaker for 5 to 20 minutes before a spontaneous beat was reestablished.

Sixteen to 64 mg. per kilogram of intravenous quinidine gluconate was given to 12 dogs, 6 of which had had an acute complete heart block established surgically a few minutes before. Nine of the dogs showed a fall of blood pressure with continuing QRS complexes in the electrocardiogram. As with similar cases in the other two forms of arrest, ventricular stimulation did not in any way change the course. All died despite pacemaking attempts. In the other three animals, one of which had a previous surgical heart block, sudden complete ventricular asystole occurred (fig. 6A), with an isoelectric electrocardiogram except for P waves. Within a few seconds an extreme ventricular bradycardia developed and stabilized at 5 to 10 per minute (fig. 6A-2). After a minute or two pulse vigour began to deteriorate. It was possible to provoke additional ventricular contractions at this time by poking the ventricles with the tip of a finger. In these three animals, ventricular pacemaking at 50 to 100 per minute was conducted for 15 to 60 minutes before the hearts established sufficient automaticity to maintain life, sustaining rates (A-4) of 24 to 39 per minute. Frequent tests were made (A-3) to determine if the heart could initiate its own beats and when this occurred, the stimulator was permanently turned off.

It is self-evident that the only condition in which an electrical pacemaking needle could aid in cardiac resuscitation would be a primary defect in the initiation of ventricular excitation. The pacemaking current as used in this study has no potentiality beyond depolarizing a trigger zone of myocardium from which the wave of excitation might spread, causing general myocardial contraction. The ideal experi-

mental environment for the use of such a pacemaking instrument would be complete ventricular asystole with a relatively normal myocardium. In our hands, as indicated, these conditions were imperfectly realized in only 6 of 45 cases of cardiac arrest. In this small group repetitive ventricular stimulation exerted a beneficial effect.

The most impressive feature of the other 39 arrests was the tenacity with which organized ventricular electrical activity persisted long after effective or even easily discernible myocardial contractions had ceased. It would have been surprising if repetitive stimulation of such hearts could exert any helpful therapeutic effect, for it merely furnishes what is already present, namely a pacemaking mechanism. Under such circumstances, the only hope for survival lies in the standard measures which are aimed at restoring myocardial contractility —massage and appropriate drug therapy.

Discussion

The complete heart block preparation affords unusual conditions for studying ventricular function during ectopic ventricular stimulation. It was observed long ago[17, 18] and in the present study as well, that serial ectopic ventricular beats caused inhibition of spontaneous impulse initiation in animals with idioventricular rhythm. It is thus possible, by stimulating the ventricle at faster than existing rates, to usurp and retain absolute control of the heart without interference from spontaneous impulses such as were demonstrated when stimulating the ventricles in the face of an intact conduction system.

The effect of such controlled rate augmentation in animals with complete heart block deserves comment. The changes in cardiac output with ventricular stimulation are essentially a reversal of the changes demonstrated in recent work on the physiology of acute heart block in dogs. It was shown[16] that reduction of rate down to 90 per minute was without significant effect on cardiac output because of larger stroke volumes at the slower rates. However, when the rate fell below 90 per minute, increases of stroke volume ceased and the cardiac output was reduced roughly as the fraction expressed by the ratio of idioventricular rate divided by 90.

In a recent study by Sarnoff and Berglund[19] concerned with *in vivo* analysis of Starling's law in dogs with a normal myocardium, it was disclosed that no descending limb could be demonstrated in the curves drawn by plotting auricular pressures against stroke work (Starling curves). With controlled elevation of auricular pressure by fluid infusion, a point was reached beyond which further elevation of auricular pressure produced neither a rise nor fall in stroke work. It is thought that under the conditions of the present study, a similar behavior is manifest. The central venous pressure is controlled in the present work by rate rather than by infusion and as the rates fall toward 90 both the venous pressure and stroke volume increase. With rates below 90 per minute, the heart is operating at maximum stroke volume on the flat portion of the Starling curve where further increases on central venous pressure are without effect on stroke work. Thus the cardiac output is placed under direct control of the rate between the range of the idioventricular rhythm and 90 per minute.

Based chiefly on work done by Wiggers,[20] it has often been suggested that ectopic ventricular beats are inherently less effective than those in which excitation is through normal routes—a concept which derives some support from the fact that patients with ventricular tachycardia decompensate more frequently than patients with auricular tachycardia at comparable rates. Wiggers states[21] that "this is due in part to a less perfect summation of fractionate contractions when the excitation waves spread from a ventricular focus, and, in part, to a less efficient mechanical twist of the ventricular muscle scrolls when the septum is not excited first".

The information obtained in the present study does not comply with this concept. In a given animal with acute heart block, approximately the same changes in cardiac output and vascular pressures are obtained irrespective of stimulation sites and without regard to their proximity to the septum. With ventricular pacemaking, stroke output tends to remain the same as it had been during spon-

aneous idioventricular rhythm despite considerable speeding of the rate. In addition, it has been shown[16] that if the ventricles are stimulated at the same rate as the heart had been beating before the block, full restoration of the cardiac output results. These findings, singly and together, suggest that stimulation of any portion of the *isolated* ventricles provokes contractions comparable in effectiveness with those initiated via the normal pathways.

Auricular and ventricular pacemaking in animals with a normal conduction system of course allows a more analogous comparison to the clinical conditions of auricular and ventricular tachycardia, respectively. In such animals in the present study, the ventricular ectopic beats were shown to be highly ineffective in comparison with the contractions evoked with similar auricular stimulation. Evidence has been presented which indicates that this inefficiency of ectopic ventricular beats is due primarily to ventricular excitation from more than one source, rather than to an inherent inferiority of the excitation or contractile mechanism of ventricular extrasystoles.

This study of experimental cardiac arrest allows several observations about the use of pacemaking therapy in cardiac standstill. From a practical point of view, myocardial failure preceded cessation of conduction in more than 85 per cent of the cases, a finding which is in accord with older studies on the selective effects of anoxia on myocardial and conduction tissue.[22] In this group, stimulation was of no value. In the remaining few arrests, there was an early complete heart block and an absence or limitation of ventricular impulse initiation. It would obviously have done no good to stimulate the auricles under these circumstances. Ventricular pacemaking was of assistance in the treatment of this group, but in half the cases had to be combined with drug therapy for recovery. It is thought that the clinical circumstances under which repetitive cardiac stimulation will be of benefit can be prognosticated from the behavior of these animals. Arrest or extreme bradycardia must have been sudden and preceded by reasonably good clinical condition. Pacemaking must be instituted immediately before the myocardium becomes unresponsive. If the chest is open, it should be possible to evoke test beats with mechanical stimulation. One must be absolutely certain that a feeble sinus-governed beat does not exist, since it was shown that even in normal hearts ventricular stimulation in the face of an intact conduction system is injurious. It is thought that occasional cases which will respond to pacemaking can be recognized. To attempt pacemaking therapy in the absence of the characteristics outlined would, however, be wasteful of time that could be better spent in the application of standard methods of cardiac resuscitation.

Summary

A study of the effects of repetitive electrical cardiac stimulation was conducted in dogs with normal hearts, complete heart block, and experimental cardiac arrest. In intact animals, auricular stimulation at faster than spontaneous rates caused alterations in cardiac output and vascular pressure explicable solely in terms of rate change. Ventricular stimulation, under similar conditions, produced injurious effects explicable primarily on the basis of double excitation of the ventricles from continuing auricular and artificial ventricular sources.

In animals with acute heart block, cardiac output is diminished because of bradycardia so extreme that an adequate compensatory increase of stroke volume is not possible.[16] Ventricular stimulation at faster rates raises the cardiocirculatory status from a low to a higher level of function as judged from measures of cardiac output and vascular pressures. In such blocked hearts, in which it is possible to have ventricular excitation solely from the stimulation site (without interference from spontaneously initiated beats), electrically induced beats compared favorably with those initiated through normal pathways.

Experimental cardiac arrest was created by asphyxia, injection of quinidine, and by chloroform inhalation to test the effectiveness of pacemaker stimulation in cardiac standstill. In more than 85 per cent of the cases, the myocardial contractility was lost long before failure of spontaneous initiation of electrical

impulses. Pacemaking was valueless in the treatment of these animals. The remaining few animals developed an early complete heart block with ventricular asystole, at a time when the myocardium retained contractile potentiality. In this small group, repetitive ventricular stimulation was therapeutically useful.

Summario in Interlingua

Electro-stimulation del corde esseva executate in canes a thorace aperte. In animales normal, stimulation auricular a frequentias plus rapide que le frequentia spontanee causava pauc cambiamento in pression vascular o rendimento cardiac. In le mesme animales un comparabile stimulation ventricular causava reductiones de rendimento cardiac e de pression sanguinee con elevationes del pression venose. Per contrasto, in animales con complete bloco cardiac le stimulation ventricular causava elevationes de rendimento cardiac e de pression sanguinee e reductiones del pression venose. Esseva etiam executate un studio de stimulation repetitive in arresto experimental del corde. In alicun casos electro-stimulation repetitive esseva de valor in le resucitation, sed le plus frequentemente il non esseva possible inducer efficace contractiones per iste medio.

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CLINICAL PROGRESS

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Primary Tumors of the Heart

By HENRY P. GOLDBERG, M.D. AND ISRAEL STEINBERG, M.D.

RECENT advances in surgical technics make it highly probable that intracavitary cardiac tumors will be successfully removed. In view of the rarity of antemortem diagnosis of these tumors it is desirable to analyze the clinical features and to call attention to an effective method of diagnosis. In addition, primary cardiac tumors involving the myocardium and pericardium will be reviewed.

Primary tumors of the heart are rare. Autopsy incidence is only 0.0017 per cent from a study of 480,331 cases.[1] Tumors of the heart have been classified as either metastatic or primary. Although many metastatic cardiac tumors are recognized clinically, therapy is limited. In a few instances x-radiation has been temporarily beneficial. Primary cardiac tumors may be classified histologically or by location. Clinically, the localization of the tumor is of paramount interest. The clinical features will depend on whether the tumor is largely within the cardiac chambers or involves the myocardium or pericardium.

INTRACAVITARY TUMORS

Intracavitary tumors originate almost exclusively in the atria. The most characteristic clinical picture is that of stenosis or regurgitation or both at the mitral or tricuspid valves with no history of antecedent rheumatic fever. The growing tumor interferes with valvular function or mechanically obstructs the orifice of the valves. Exertional dyspnea is common and when cardiac failure develops, it is usually intractable because of the mechanical interference with atrial or ventricular filling. Cardiac output is severely reduced and may result in the development of angina. Systolic blood pressure is often low. Fragmentation of tumor or dislodgement of surface thrombi may lead to clinical signs of embolization. In some patients there may be definite knowledge of the absence of murmurs until the onset of the illness. Other features include arrhythmias, syncope, unexplained episodes of dyspnea, cyanosis, orthopnea and variation in symptoms and auscultatory signs with change of position of the patient.

Cardiac catheterization data are available in seven patients in whom the diagnosis of myxoma has been proved; one with a right atrial myxoma[2] and six with left atrial myxoma.[3-7] In all seven cases there was evidence of obstruction to outflow from the atria. This consisted of abnormal elevation of atrial pressure. In the left atrial tumors, the pulmonary capillary pressures were elevated in five patients. Cardiac output was reduced in the patient with the right atrial tumor; normal, in one patient with a left atrial tumor; and reduced, before or after exercise, in four of the others. It is doubtful that the catheterization data can be interpreted as revealing more than interference with atrial emptying. However, in the patient reported by Bayer and coworkers[8] the catheterization data suggested the presence of a mass at the tricuspid valve. This is not a proven case although the angiocardiogram suggested a right atrial tumor.

Angiocardiography has proved to be the

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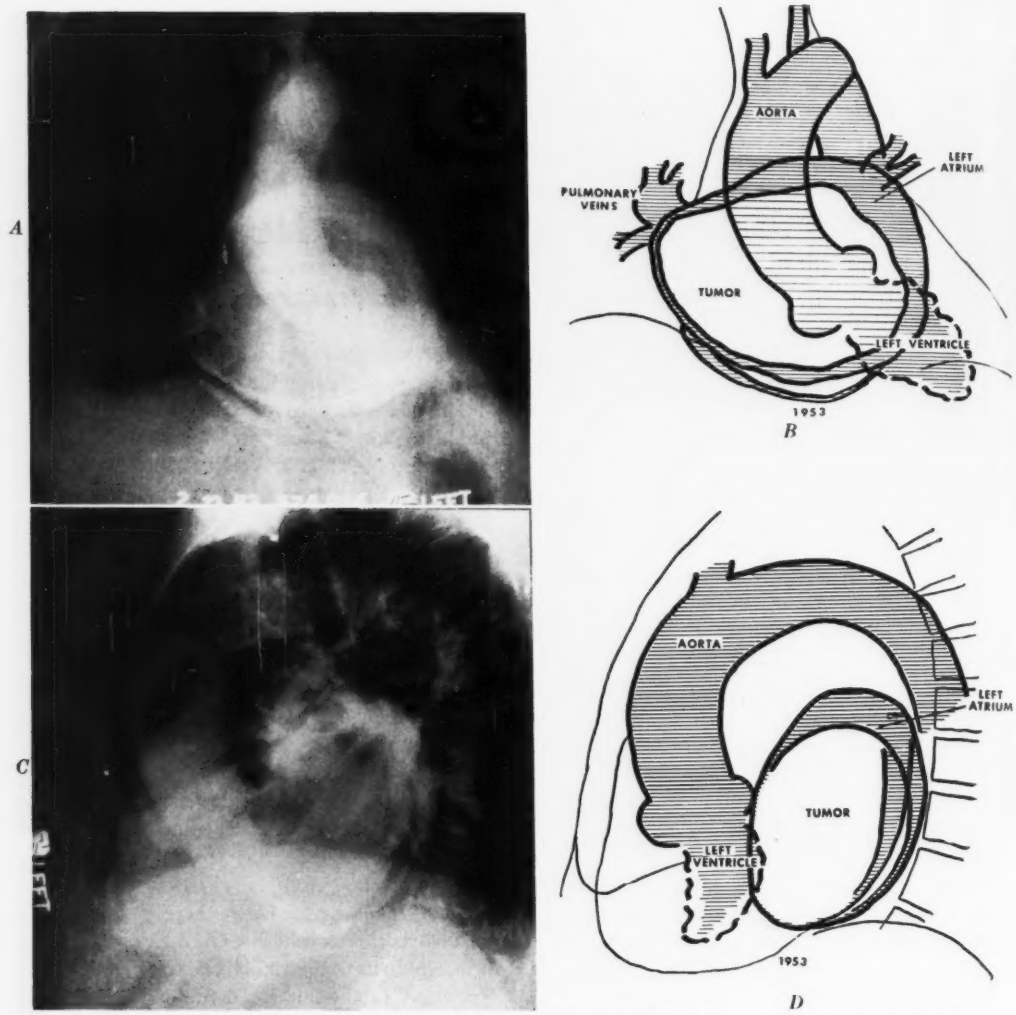
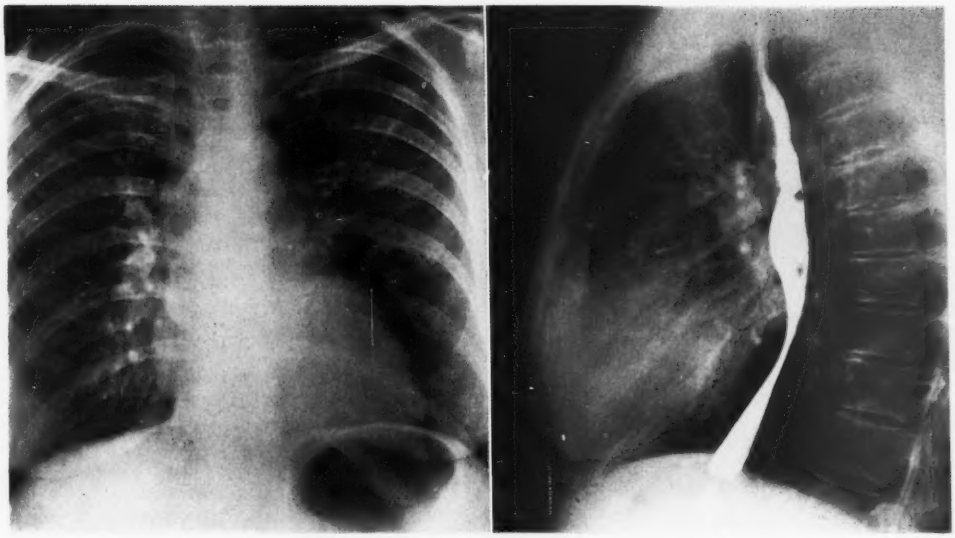


FIG. 1. *Left atrial myxoma.* A 53 year old woman, with an atypical history consisting of exertional dyspnea, weakness and palpitation for 26 years, had enlargement of the right heart and left atrium without murmurs. *A* and *B*. Frontal angiocardiogram at 11 seconds and tracing. *C and D*. Lateral angiocardiogram at 11½ seconds and tracing (previously published[3]).

definitive method for diagnosis of intracavitary tumor. Characteristic persistent filling defects in an enlarged atrium were noted in all cases (figs. 1 and 2).[2, 3] In the three patients with left atrial myxoma[3] a point of attachment of the tumor to the atrial septal wall was clearly visualized. Mural thrombi in the atrium do not produce filling defects in the angiocardiogram.[9] Filling defects due to the regurgitant stream in tricuspid insufficiency are transient. Angiocardiography of a patient with an atrial obstructing thrombus (ball-valve or pedunculated) has not been reported. It is probable that such a thrombus will produce similar roentgen findings. Fortunately, exact differentiation is of no consequence since surgery should be considered for both the thrombus and the tumor.



A *B*

2*A and B*. Frontal and lateral chest x-ray films illustrate slight prominence of the pulmonary segment and esophageal indentation by a large left atrium (previously published[3]).

FIGS. 2, 3 *and* 4. *Left atrial myxoma.* A 46 year old woman, in previous good health, had a sudden attack of cough, dyspnea, chest pain and palpitation on stooping. There was evident heart failure and presystolic and systolic apical murmurs were noted. The presystolic murmur disappeared when the patient was supine.

The cardiac intracavitary tumors are of two types. The myxoma is the most common and in fact comprises 50 per cent of all primary cardiac tumors. It has been reported in patients from the age of 3 months to 68 years, the majority occurring between 30 and 60 years in equal sex distribution. The myxoma generally arises by a small pedicle from the atrial septum in the region of the fossa ovalis. About 75 per cent of these tumors occur in the left atrium; extra-atrial location being rare. The tumors are variable in size and may be so small as to cause no symptoms, and sometimes are discovered incidentally at autopsy. Although there has been controversy as to whether the myxoma is a neoplasm or a thrombus, prevailing opinion holds that it is a benign tumor. Strong evidence for the neoplastic nature of the myxoma is provided by a recent study reporting growth of a myxoma fragment in the mesenteric arteries and brain.[10] This suggests that a myxoma is potentially malignant but none of the other reported cases showed lymphatic or hematogenous spread, local invasiveness or mitotic cells. They are generally smooth, pedunculated or villous, whitish tumors of variable consistency. There may be areas of hemorrhage and occasional overlying thrombi. Microscopically, the tissue is rather poorly cellular with an endocardial covering. Multinuclear and stellate cells and focal collections of plasma cells and lymphocytes have been noted. Cysts, bone and collagen deposition have been described.

The other variety of intracavitary cardiac tumor consists of sarcomas of all histological types. Although sarcomas are predominantly mural tumors they are discussed here because the presenting symptoms are frequently due to intracavitary extension. Age and sex distribution are the same as for myxoma. The sarcomas involve the right side of the heart more frequently and are polypoid in about 20 per cent. Unlike the myxomas, they involve the ventricles as often as the atria. The clinical picture produced by the intracavitary cardiac

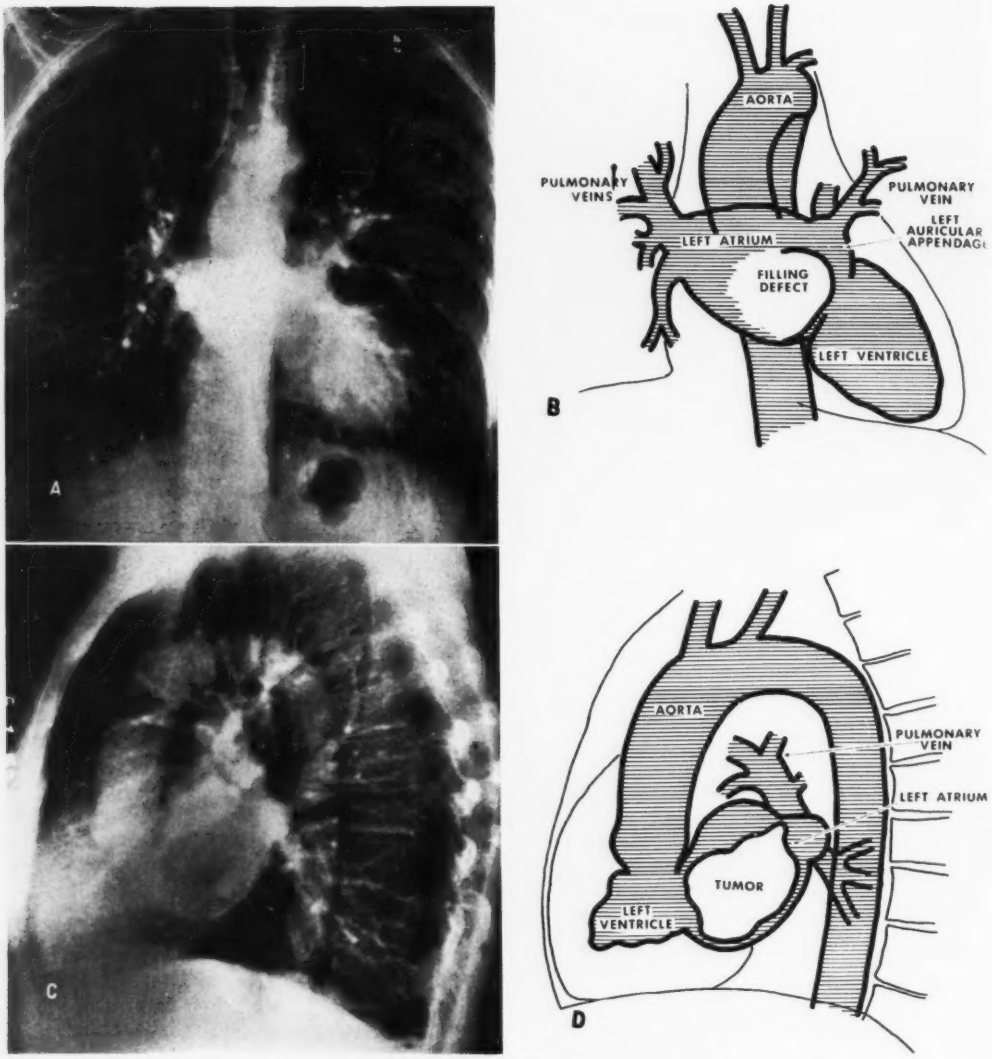
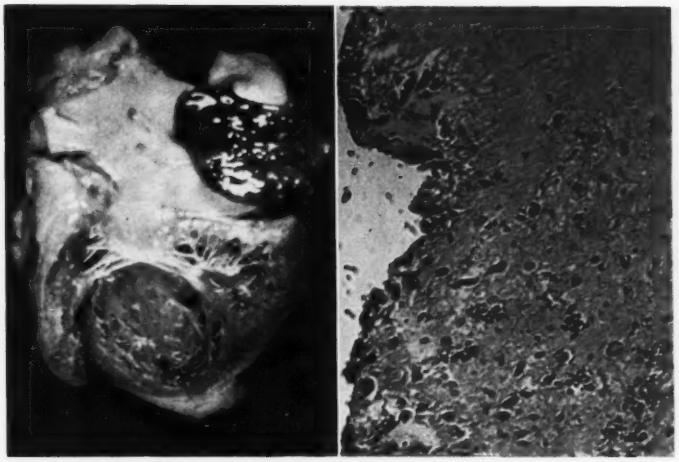


FIG. 3*A and B*. Same patient referred to in figure 2. Frontal angiocardiogram at 13 seconds and rtacing (previously published[3]). *C and D*. Lateral angiocardiogram at 13 seconds and tracing (previously published[3]).

sarcomas may resemble that due to myxoma, except for the frequent occurrence of hemopericardium, arrhythmias and the more common development of inferior and superior vena caval obstruction. These tumors grow rapidly. Five cases have been diagnosed antemortem. Approximately 25 per cent of Wharton's 100 cases[11] showed no metastases at necropsy and of these there were seven polypoid atrial tumors.

MURAL TUMORS

Tumors involving the heart wall or valves, such as angiomas, hamartomas and nodular rhabdomyomas, have for the most part been reported as incidental autopsy findings. A few



A *B*

FIG. 4. Same patient referred to in figure 2. *A*. Photographs of gross specimen. *B*. Photomicrograph ×200 of myxoma.

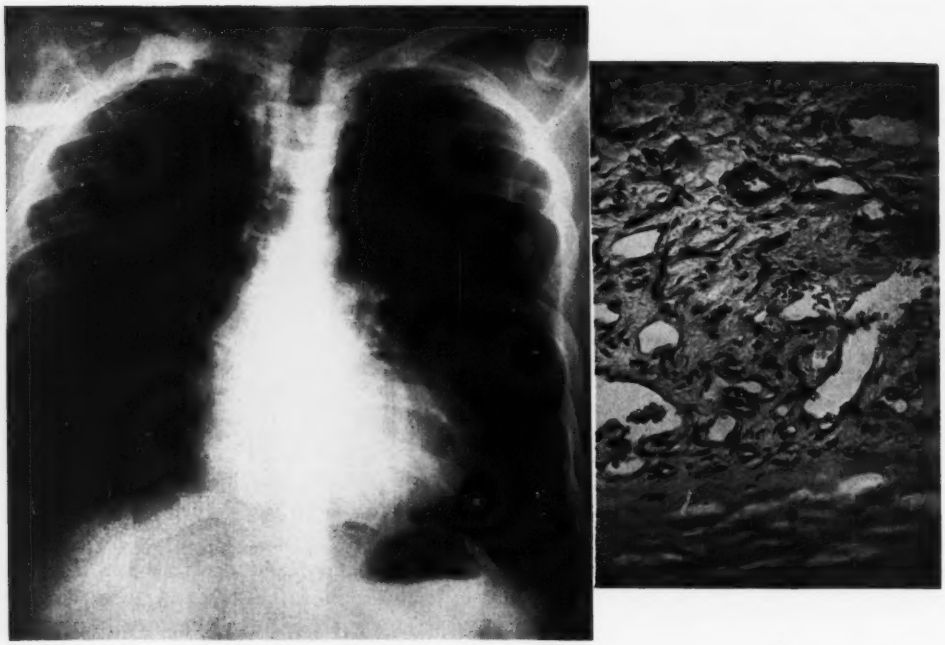
strategically placed have caused arrhythmias, interference with coronary blood flow and sudden death.

PERICARDIAL TUMORS

The benign pericardial tumors are rare; only about one-fourth as frequent as benign tumors of the heart, per se. Among the reported cases are teratomas, fibromas, lipomas, angiomas, cysts and leiomyofibromas. Although these tumors usually arise from the myocardium (fig. 5) or embryonic rests, they expand into the pericardial cavity.[12] Many are discovered because of a chance x-ray demonstration of an unusual heart contour. In others, the sudden appearance of symptoms is due to the development of a hemorrhagic pericardial effusion. This occurs almost as frequently in benign as in malignant pericardial tumors. The malignant pericardial tumors produce a more rapid course, are associated more often with chest pain and dry cough and in one-third of the cases pulmonary metastases are seen. Electrocardiographic signs are of little help in either suggesting or confirming the presence of a primary pericardial tumor since the changes usually reflect an effusion. Diagnostic artificial pneumopericardium in the presence of an effusion has been strongly advocated by Mahaim.[13] Examination of pericardial fluid for tumor cells has led to the diagnosis in a few cases. Angiocardiography may demonstrate a unilateral pericardial mass.[12, 14, 15]

DIAGNOSIS

The symptoms which may be produced by primary cardiac tumors are so much more frequently due to other lesions that the diagnosis will depend chiefly on a sharp awareness of the possibility. The left atrial tumor must be looked for in the patients who present symptoms and signs of obstruction of the lesser circulation. Signs of mitral stenosis not dating from birth in young children,[16] absence of cardiac difficulties until the onset of intractable heart failure, inconstancy of mitral murmurs, and episodes of syncope or cyanosis and dyspnea without adequate explanation except for change in position are important clues. Any of these findings should lead to angiocardiography. Some patients with left atrial tumors will mimic rheumatic mitral stenosis so completely as to escape detection unless angiocardiography is used routinely in the evaluation of all patients being considered for mitral valvulotomy. At present routine preoperative angiocardiography is not advocated.[17] The need for exact preoperative diagnosis of a left atrial tumor is more than



A *B*

FIG. 5*A*. *Hemangioma of the left ventricle*. The frontal angiocardiogram of a 25 year old man who had precordial pain, dyspnea and palpitation. It illustrates a nonfilling oval mass at the left cardiac border. *B*. Photomicrograph of the biopsy specimen reveals a sclerosing hemangioma attached to the heart wall. (Courtesy Dr. Harold A. Lyons)

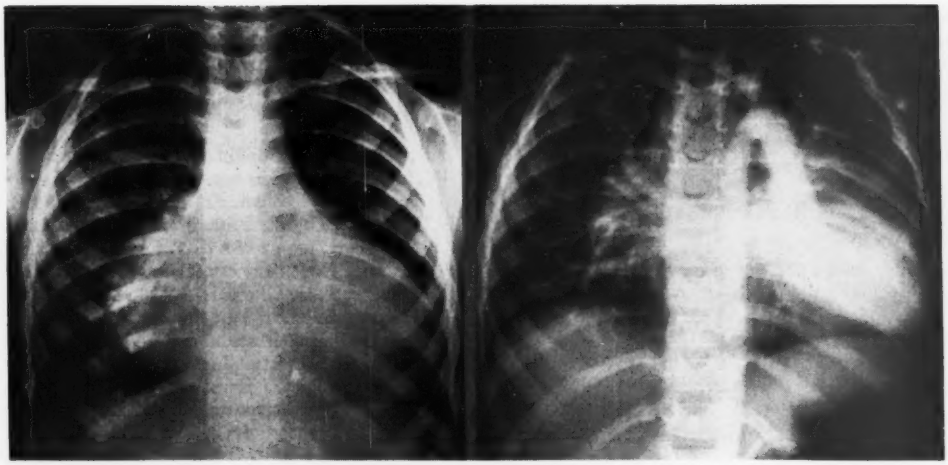
academic since successful surgery may require an open technique (figs. 1–4).[2, 3]

Tumors of the right side of the heart will be found in patients who present signs of inflow stasis, which include dyspnea, orthopnea, dilated neck veins, facial edema, cyanosis, hepatomegaly, ascites, dependent edema, pleural effusion and increased venous pressure. Preliminary diagnoses will include constrictive pericarditis, tricuspid stenosis and insufficiency, pericardial effusion, superior vena caval syndrome and chronic congestive heart failure. The differential diagnosis of these conditions is often difficult even with the aid of a battery of laboratory examinations. Angiocardiography, in this situation will demonstrate the presence of a cardiac tumor as well as aid in the differentiation of the other conditions.

The diagnosis of primary pericardial tumors depends on the discovery of an unusual cardiac contour which is not readily explained. There are no diagnostic clinical or laboratory criteria which will differentiate pulmonary and mediastinal masses adjacent to the heart from intrapericardial tumors. If the presence of a pericardial effusion can be established, examination of the fluid may lead to diagnosis of tumor. In general the diagnosis will await surgical exploration and biopsy (fig. 5).[12] However, it is possible that visualization of cardiovascular rotation, as opposed to displacement in the angiocardiogram, as demonstrated in a unique case of intrapericardial tumor[15] may provide a significant differential sign (fig. 6).

TREATMENT

Exclusive of pericardial cysts, which have been removed on many occasions, successful surgery of benign intrapericardial tumors has been reported only four times. In 1942, Beck[18] presented a case of an intrapericardial teratoma which he removed in two stages. Eight years



A *B*

FIG. 6. *Intrapericardial bronchogenic tumor.* An asymptomatic 3 year old girl had a marked chest deformity, unusual cardiac silhouette and no murmurs. *A*. Frontal chest x-ray illustrates the apparent cardiac enlargement. *B*. Frontal angiocardiogram at 6 seconds shows rotation of the left ventricle and aorta. Earlier films revealed a nonopacified intrapericardial mass.

later Hochberg and Robinson[19] removed an intrapericardial cavernous hemangioma which was partly adherent to the myocardium. Maurer[12], in 1952, reported the removal of a large intrapericardial lipoma which arose by a small pedicle from the left ventricular wall. In 1953, Miscall[15] successfully operated on a 3 year old child who had a large bronchogenic tumor in the pericardial cavity. These four reports reflect the rarity of intrapericardial tumors and illustrate the effectiveness of surgical treatment.

In his paper Beck also had suggested the possibility of removal of intra-atrial tumors. Mahaim in 1945[13] extensively reviewed the literature on cardiac myxoma and concluded that the architecture of the tumor made surgical removal feasible. He emphasized the clinical features and predicted the role of angiocardiography in arriving at the diagnosis. Six cases of intra-atrial myxoma have been diagnosed during life. One of these[20] was operated on with the aid of hypothermia but the patient died of ventricular fibrillation during the procedure. Bahnson[2] succeeded in removing most of a right atrial myxoma and the patient lived for 24 days after operation. Death was due in part to obstruction of the inferior vena cava by residual tumor. In two cases,[3] attempted removal of the left atrial myxomas through the auricular appendage was unsuccessful; death occurred during surgery. One patient (figs. 2, 3 and 4) was explored but the small size of the auricular appendage prevented an attempt at removal of the tumor. Surgery was not performed on Kirkeby and Lerens' patient.[21] In addition, several myxomata have been found during surgery for mitral stenosis or constrictive pericarditis[2, 7] but attempted removal met with failure in all.

Clowes' patient[22] was found to have a left atrial tumor during surgery for presumed rheumatic mitral stenosis. Surgical removal of the tumor was considered too hazardous. Six months later, after several episodes of severe pulmonary edema, an open procedure with the use of a pump oxygenator to bypass heart and lungs, was carried out. The patient died six hours after operation.

After this review was completed the following communication was received from Crafoord.[23] "I can inform you that after exact anatomical diagnosis due to selective cardioangiography, on July 16, 1954, we operated on a case of pseudomyxoma of the left atrium, the size of a small orange, with the aid of

complete bypass with extracorporeal oxygenation and circulation produced by our own pump-oxygenator. The blood was shunted from the cavae to the aorta through the left subclavian artery. During the 28 minutes of exclusion of the heart from the circulation and the intracardiac manipulations the heart was in a state of ventricular fibrillation intentionally brought about by electrical stimulation in order to facilitate the extracorporeal circulation and the actual technical procedure within the heart. After closure of a maximal wide incision in the left atrium, the heart was electrically defibrillated. The postoperative period was somewhat disturbed by a slight rise in both nonprotein rest urea in the blood and a moderate elevation in the bilirubin. This healed otherwise without complications and the patient is now considered completely recovered. Before the operation, the patient had the usual symptoms of paroxysmal mitral occlusion and mitral stenosis which now no longer are present."

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ABSTRACTS

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BALLISTOCARDIOGRAPHY

Dock, W.: The Value of Lateral Ballistocardiograms in Differentiating Aortic Tortuosity from Myocardial Infarction. Am. J. M. Sc. **228:** 125 (Aug.) 1954.

A recording platform for the measurements of forces in the head-foot, lateral and dorsoventral planes is described which obtains ballistic waves in one simple operation. The head-foot force is transmitted along the axial skeleton and can be inscribed from the table or from the patients' shins. Lateral or front-back forces must be recorded from the thorax since they are not transmitted well to the table. Normally in young people the lateral waves are ¼ to ½ as great as the head-foot deflections. The lateral tracings revealed that, in many cases, a decrease in the head-foot systolic waves is paralleled by an increase in the lateral waves. This indicates that the direction, but not the force, of ejection is changing. Tortuosity of the aorta appears to be the major factor resulting in a large lateral with a small head-foot wave. The lateral ballistocardiogram reveals large diastolic waves due to gallop phenomenon or auricular systole, not apparent in the classical tracing. The effects of respiration, drugs, and various types of heart disease on the combined tracings are presented.

SHUMAN

Simon, D. L., Iglauer, A., and Braunstein, J.: The Immediate Effect of Cigarettes on the Circulation of Healthy and Habitual Male Smokers. Am. Heart J. **48:** 185 (Aug.) 1954.

The immediate effect of smoking regular and low-nicotine filtered cigarettes was studied in 14 young males. Cardiac outputs (ballistocardiogram), pulse rates (electrocardiogram) and skin temperatures (thermocouple) were determined. The results indicated that although smoking constricted peripheral vessels, causing increase in heart rate and fall in skin temperature, the effect was not strong enough to change the form of the ballistocardiogram or affect the cardiac output, except in cases of individual susceptibility or sensitivity.

MAXWELL

BACTERIAL ENDOCARDITIS

Johnson, T. D., and Hurst, J. W.: Bacterial Endocarditis Due to a Penicillin-Resistant Staphylococcus. Report of a Case Successfully Treated with Erythromycin, Oxytetracycline and Streptomycin. New Eng. J. Med. **251:** 219–221 (Aug. 5) 1954.

A boy aged 3 years with an interventricular septal defect complicated by subacute bacterial endocarditis due to a Penicillin resistant staphylococcus aureus is described. Massive doses of Penicillin, 30,000,000 to 60,000,000 units intravenously, together with 0.25 gm. of Streptomycin intramuscularly daily seemed to have no appreciable effect during the first five days of treatment. Improvement did appear when Erythromycin, Oxytetracycline and Streptomycin were given, particularly after diarrhea and incomplete absorption led to intravenous administration of Oxytetracycline and large doses of Erythromycin. Erythromycin was given by constant intravenous infusion in doses of 2 gm. daily through a polyethylene venous catheter with booster doses of 250 mg. intravenously every 8 hours together with 1 gm. of Oxytetracycline intravenously daily. These drugs were given for 10 weeks, although intravenously for only two weeks. This is believed to be the largest reported quantity of Erythromycin given intravenously, on the basis of body weight. The organism was inhibited in vitro by concentrations of Penicillin which were exceeded in vivo but

there was no clinical response to this drug. Furthermore, the organism was cultured when the patient was receiving moderate doses of Erythromycin, a drug which proved beneficial in much larger doses. The experience in this case is felt to suggest a synergistic effect of other antibiotic agents with Erythromycin.

ROSENBAUM

BLOOD COAGULATION

Waldron, J. M., and Duncan, G. G.: Variability of the Rate of Coagulation of Whole Blood. Am. J. Med. **17:** 365 (Sept.) 1954.

Variations in technic of obtaining the sample of blood and in measuring the rate of coagulation are only partly responsible for the variability of the whole blood clotting times. Some of the variability is due to the in vivo effect of exogenous and endogenous factors affecting the circulating blood. With a standard technic the rate of clotting of whole blood is remarkably constant in the same individual on the same day or on different days, if the individual is studied under conditions which keep the variability of endogenous and exogenous factors at a minimum. The basal state is the best condition in which to study the rate of clotting of whole blood because the variations in endogenous and exogenous factors are at a minimum.

Ingested fat in the form of cream or butter accelerates the rate of coagulation of whole blood. The response is detectable in one-half hour after ingesting the fat and reaches a maximum in one hour. Thereafter, the effect progressively diminishes. This results in a constant and characteristic biphasic curve of response. The accumulation of thrombin on glass does not explain this phenomenon. Evidence is presented that adequate washing in running water and saline permits the reuse of a syringe without influencing the results. Sterilization of syringes, pipettes and test tubes used in the measurements of the rate of blood coagulation is unnecessary.

HARRIS

Quick, A. J., Georgatsos, J. G., and Hussey, C. V.: The Clotting Activity of Human Erythrocytes: Theoretical and Clinical Implications. Am. J. M. Sc. **228:** 207 (Aug.) 1954.

Washed human erythrocytes were hemolyzed in the absence of platelets and were found to produce a clotting factor in the hemolysate, causing a high consumption of prothrombin when added to normal plasma. The prolonged prothrombin time of serum obtained after clotting of the human plasma was shown to be due to a decrease in prothrombin and not to a lack of proconvertin. The erythrocyte hemolysate was inactive when added to hemophiliac plasma indicating that it requires thromboplastinogen for its clotting action. In very mild hemophilia, the escape of this clotting factor from erythrocytes may bring the consumption of prothrombin time into the normal range. The prothrombin consumption test has been shown to be more reliable when carried out on platelet-rich plasma than on whole blood. The pressure of the erythrocyte clotting factor is believed to be the explanation for the poor results obtained with this test as applied to whole blood in mild hemophiliacs. The physiological significance of this newly-found clotting factor remains to be determined.

SHUMAN

Clatanoff, D. V., Triggs, P. O., and Meyer, O. O.: Clinical Experience With Coumarin Anticoagulants Warfarin and Warfarin Sodium. Arch. of Int. Med. **94:** 213 (Aug.) 1954.

Intravenous warfarin sodium induced therapeutic hypoprothrombinemia safely and effectively in 20 patients. Warfarin or warfarin sodium orally induced an effective hypoprothrombinemia in 16 patients, with a similar time of onset and duration. The initial dose for either drug was 1 mg. per kilogram of body weight; however, the authors now conclude that an initial dose should not exceed 75 mg., regardless of body weight. There would appear to be no advantage to use of warfarin sodium intravenously rather than warfarin or warfarin sodium orally, except when the patient is vomiting or cannot otherwise tolerate oral medication.

Maintenance of therapeutic hypoprothrombinemia was accomplished with ease in 21 patients by using warfarin or warfarin sodium orally. Warfarin appears to have no advantage over warfarin sodium. As with other 4-hydroxycoumarin compounds, microscopic hematuria is occasionally seen as a toxic manifestation, and one must watch for this as well as other evidences of hemorrhage. Vitamin K_1 is a very effective antidote against hypoprothrombinemia induced by warfarin sodium and warfarin.

BERNSTEIN

CONGENITAL ANOMALIES

Magidson, O., Cosby, R. S., Dimitroff, S. P., Levinson, D. C., and Griffith, G. C.: Pulmonary Stenosis with Left to Right Shunt. Am. J. Med. **17:** 311 (Sept.) 1954.

The authors report a series of 14 cases presenting pulmonary stenosis of mild or moderate degree with little or no increase in right atrial or right ventricular diastolic pressure, associated with atrial septal defect, ventricular septal defect, or transposed pulmonary veins permitting a left to right shunt. The clinical features were generally those of mild or moderate pulmonary stenosis with electrocardiographic or radiologic findings suggestive of an accompanying septal defect. The signs of dynamically severe stenosis—cardiac enlargement, precordial heave, pure second sound, prominent "a" wave in the neck, hepatic pulsation and small volume arterial pulses—were usually absent. The electrocardiogram frequently showed a right bundle

branch block pattern slightly favoring the presence of a septal defect. Radiologically, dilatation of the pulmonary artery segment was in keeping with a valvular pulmonary stenosis, while the evidence of an increased pulmonary blood flow pointed to a left to right shunt. Clinical differentiation between the different types of shunt was not especially sought but a low murmur and thrill would appear to favor the presence of a ventricular septal defect. In all eight cases of pulmonary stenosis and atrial septal defect fluoroscopic examination of the site of pressure change and the appearance of the records suggested that the stenosis was valvular in all cases. The stenosis was always mild or moderate with a right ventricular systolic pressure well below 100 mm. Hg and a normal or even slightly elevated pulmonary artery pressure. The right atrial pressure was normal in all cases, averaging 2.5 mm. Hg. Measurement of left atrial pressure in five cases indicated that the pressure gradient across the atrial defect necessary to maintain an over-all left to right shunt was present.

The question of the inadvisability of pulmonary valvulotomy in these cases is discussed.

HARRIS

Lukas, D. S., Araujo, J., and Steinberg, I.: The Syndrome of Patent Ductus Arteriosus with Reversal of Flow. Am. J. Med. **17:** 298 (Sept.) 1954.

Pulmonary arterial hypertension of sufficient magnitude to cause shunting of venous blood from the pulmonary artery into the aorta (mainly the descending portion) is the underlying basis for the physiologic and clinical features in four newly investigated cases of patent ductus arteriosus with reversal of flow, and twelve cases selected from the literature. The pulmonary hypertension is related to extensive arteriosclerotic and thrombotic alterations in the medium and small-sized pulmonary arteries.

Clinical diagnosis of patent ductus arteriosus with reversal of flow is made by the discovery of cyanosis and clubbing of the toes and absent or less pronounced cyanosis and clubbing of the fingers. Right ventricular hypertrophy is also present roentgenologically and electrocardiographically. Angiocardiography and cardiac catheterization establish the diagnosis unequivocally, are of aid in excluding coexisting defects and provide information needed in decisions concerning ligation of the ductus. Limited surgical experience indicates that ligation of the ductus is hazardous but may be followed by considerable decrease in the pulmonary hypertension.

The usual clinical characteristics of uncomplicated patent ductus arteriosus are absent; the continuous murmur is not heard; and the pulmonary blood flow is small. Patients demonstrating the syndrome of patent ductus arteriosus with reversal of flow (shunting of blood from the pulmonary artery to aorta of sufficient magnitude to cause cyanosis) are not necessarily in cardiac failure and may live for many years after its onset.

HARRIS

Bjork, V. O., Crafoord, C., and Varnauskas, E.: Closure of an Atrial Septal Defect and Pulmonary Valvulotomy in a 49-year-old Man. Ann. Surg. **140:** 212 (Aug.) 1954.

The authors described a new approach to the treatment of inter-atrial septal defects which was used in 12 cases, with 10 survivals. The procedure consisted of introducing a big, curved needle at the base of the aorta, which was guided in the septal rim down through the upper portion of the interventricular septum and out behind the aorta. The sutures were then drawn taut over a piece of muscle from the chest wall to avoid their cutting through the thin atrial wall in the dissected groove.

ABRAMSON

Thomas, W. A., Randall, R. V., Bland, E. F., and Castleman, B.: Endocardial Fibroelastosis: A Factor in Heart Disease of Obscure Etiology. A Study of 20 Autopsied Cases in Children and Adults. New Eng. J. Med. **251:** 327–338 (Aug. 26) 1954.

This report is concerned with 20 cases of endocardial fibroelastosis found in a series of 10,000 autopsies at the Massachusetts General Hospital since 1930. Four cases were infants, aged 2 years or less, four patients were children aged 5 to 11 years, and the remaining 12 cases ranged in age from 16 to 71 years. The infantile group was characterized by marked cardiac hypertrophy, marked generalized fibroelastic proliferation of the endocardium overlying normal myocardium in most areas and only minimal, spotty myocardial fibrosis, when present. The foramen ovale was closed in all cases and these authors support the view that this disorder is congenital in origin. The childhood cases were identical with those in the infantile group except that there was less endocardial thickening and less striking hypertrophy; symptoms also appeared at a later age. The childhood cases are also believed to be congenital in origin. The adult cases showed fibroelastic endocardial thickening which was qualitatively identical with that in childhood, in some as severe and in others less severe and more patchy in extent. When the clinical picture in the adults was contrasted with that in children it was found that the average duration of symptoms was much longer, congestive failure was more prominent, mural thrombi were present in three-quarters of the patients and embolization was very frequent. A familial history of fatal heart disease was also common. The adult cases are also felt to be, in all probability, congenital in origin.

This disorder is differentiated by these authors from Beri-beri, heart disease, myocarditis, East African endomyocardial necrosis and the "Collagen"

diseases. The endocardial fibroelastosis is believed to produce clinical symptoms by (1) endocardial constriction, (2) interference with proper conduction of contraction impulses, or (3) interference with the blood supply of the muscle underlying the involved endocardium with resultant anoxia.

ROSENBAUM

Braun, K., Milwidsky, H., Izak, G., and Schor, S.: Pulmonary Hypertension in Patent Ductus Arteriosus Relieved by Surgery. Angiology **5:** 329 (Aug.) 1954.

A detailed case report is presented of a 13 year old girl with patent ductus arteriosus associated with marked pulmonary hypertension and intermittent reversal of the shunt. At operation the pulmonary artery pressure dropped from 75/60 mm. Hg to 50/40 mm. Hg when the ductus was occluded. Because of this finding, the ductus was divided. Cardiac catheterization eight months after operation showed that the pulmonary artery pressure was 32/12½ mm. Hg. The drop in pulmonary pressure was paralleled by marked clinical improvement. The authors believe that in this patient the high pulmonary resistance was related to the blood flow through the patent ductus.

WESSLER

Shumacker, H. B., Jr.: Experimental and Clinical Observations on the Closure of Cardiac Septal Defects. Angiology **5:** 289 (Aug.) 1954.

Procedures for the repair of atrial and ventricular septal defects are described and the results in animals and in several human patients reported. The author believes that the repair of atrial septal defects by the method described have been sufficiently successful to deserve more extensive clinical trial. The repair of ventricular septal defects, although appearing to be technically sound, will require further experience before it can be considered safe and practical.

WESSLER

CONGESTIVE HEART FAILURE

Clinico-pathologic Conference: Amyloidosis of the Liver and Cardiac Failure. Am. J. Med. **17:** 280 (Aug.) 1954.

Discussion centers about the medical problems of a fifty year old white male with refractory heart failure whose post-mortem examination disclosed primary amyloidosis of the heart, spleen, adrenals and vessels of the kidneys, liver, pancreas and prostate with cardiomegaly and splenomegaly. A liver punch biopsy led to the correct ante-mortem diagnosis.

Amyloidosis may be classified as primary or secondary types. The secondary type is associated with some underlying disease. Perhaps 80–90 per cent of patients with secondary type of amyloidosis suffer from tuberculosis; the remaining 10–20 per cent of cases occur in association with pyogenic lesions of bones such as osteomyelitis, and suppurative diseases of the lung.

Primary or systemic amyloidosis is characterized by involvement of blood vessels, particularly the small arteries. In primary cardiac amyloidosis the amyloid deposits are almost entirely localized in the heart. Primary amyloidosis, like the secondary type, affects the liver, spleen and kidneys. Of all the criteria for the diagnosis of primary systemic amyloidosis absence of preexisting or etiologic disease is the only constant clinical and pathologic finding. The usual Congo red test performed over a sixty minute period may be quite inaccurate. It is recommended that this test be performed over 30 minutes and that several values should be determined. The results should then be extrapolated on a semilog curve back to 0. Gingival biopsy may be of value when primary amyloidosis is suspected.

All layers of the heart may be involved, particularly the endocardium. Extensive deposits of amyloid in the mitral and aortic valves may produce significant valvular defects.

HARRIS

CORONARY ARTERY DISEASE

Lechner, E., Nunez, H., Nemir, P., Jr., and Bellet, S.: A Comparison of the Tolerance of the Normal Dog and the Dog with Myocardial Infarction to an Organic Mercurial (Mercurophylline). A Study of the Serum and Muscle Electrolyte. Am. J. M. Sc. **228:** 282 (Sept.) 1954.

The administration of mercurial diuretics has been followed by manifestations of toxicity and occasionally by death. The experiments conducted by the authors compared the direct effects of organic mercurials upon the normal and damaged heart. In addition, blood, skeletal muscle and myocardium samples were obtained before and after mercurial injections for measurement of sodium, potassium and magnesium. The mercurial solution was infused intravenously in a concentration equivalent to 2.6 mg. of mercury per ml. resulting in death in all instances from 25 to 50 minutes after the beginning of the injection. Thirteen dogs were used of which five were subjected to ligation of the anterior branch of the left coronary artery. The electrocardiographic changes and lethal doses were not significantly different in the two groups of dogs. The average values of serum sodium, potassium and magnesium fell in both groups following administration of the mercurial. Skeletal muscle potassium and magnesium rose slightly after the mercurial; variations in tissue sodium concentrations were not significant. The data indicate that the effect of the mercurial is independent of the presence and the degree of heart muscle damage; nor was there any correlation between the change in potassium, sodium and magnesium levels and lethal dosage.

SHUMAN

Russek, H. I., and Zohman, B. L.: Selection of Patients for Anticoagulant Therapy in Acute Myocardial Infarction. Am. J. M. Sc. **228:** 133 (Aug.) 1954.

Of 271 cases of acute myocardial infarction seen during a period of 3 years, 122 qualified as "good risks" on the basis of the absence of certain signs of unfavorable prognostic import: previous infarction, intractable pain, severe shock, gallop rhythm, significant cardiac enlargement, arrhythmias and various conditions predisposing to thromboembolism. These "good risk" patients were not given anticoagulant therapy and were placed on a graduated program of activity. Of the 122 patients so treated 6 died during the period of hospitalization, 3 of these deaths occurring within the first 48 hours. Analysis of the causes of death showed that only one might have been prevented by anticoagulant therapy, although, in this case, the cause of death was undetermined. Clinical thromboembolic events occurred in 2 patients in the form of pulmonary embolism; 2 others were presumed to have phlebothrombosis on the basis of calf tenderness.

It is estimated that approximately 30 per cent of the patients with myocardial infarction are candidates for anticoagulant therapy. The prognosis in "good risk" cases is not significantly influenced by such treatment. The incidence of hemorrhage and death due to anticoagulant drugs outweighs the benefits derived from their use in milder cases. The initial clinical appearance of the patient, regardless of his age, is the best index of his future course and the deciding factor regarding the need for anticoagulant therapy.

SHUMAN

ELECTROCARDIOGRAPHY

Sibille, A., Kremen, R., and Lavenne, F.: Divergence between ÂQRS and ÂT in the Frontal Plane. The Limits of Normal. Arch. mal. coeur. **47:** 635 (Aug.) 1954.

The authors studied the clinical significance of the finding of an angle between the frontal QRS and T vectors. Among 1558 patients with such an electrocardiogram 171 had a complete bundle branch block, 1006 other associated anomalies in the electrocardiogram, and in 381 the divergence of the two axes was the only alteration. There were 11 subjects with clinically and roentgenologically normal hearts in the first, 73 in the last, and none in the second group. Thus in 80 per cent of the cases in which the angle between QRS and T is more than 60° the chances are that this electrocardiographic anomaly is associated with a clinical anomaly. The remaining 20 per cent present a diagnostic problem.

The following additional data derived from further analysis of the material proved helpful in the evaluation of such electrocardiograms. An angle greater than 100° is invariably abnormal. A lesser degree of divergence with ÂQRS at +55–120°, and ÂT deviated in a counterclockwise direction is always abnormal in young persons and suspect in persons over 35 years. On the other hand, ÂQRS between −40 and +55° and ÂT deviated in clockwise direction is always abnormal in persons over 35 and suspect in younger ones.

PICK

Burger, H. C., Tolhoek, H. A., and Blackbier, F. G.: The Potential Distribution on the Body Surface Caused by a Heart Vector. Calculations on Some Simple Models. Am. Heart J. **48:** 249 (Aug.) 1954.

A mathematical treatment of the dipole field in a bounded space is given for a few simple cases. The potential at the surface is calculated for an open and for a closed cylinder with the dipole on its axis, and for an infinite layer bounded by two parallel planes, the dipole being situated nearer to one plane than to the other. The medium is assumed to be homogeneous. The image surface is calculated and represented in several diagrams. A detailed appendix with the mathematical equations follows the body of the article.

MAXWELL

Luisada, A. A.: Electrocardiography in the Aged. Geriatrics **9:** 381 (Aug.) 1954.

The data supplied by the various electrocardiographic leads are described briefly. The electrocardiogram can be used for timing waves of other tracings and for evaluating atrial and ventricular rates, for ascertaining position of the heart, and in the field of myocardial and coronary heart disease. The electrocardiogram has limitations and its data should not be unduly stressed in preference to those supplied by other methods of investigation. The electrocardiogram of the aged may present minor changes of the P-R or QRS intervals or of the height of the T wave, slight left axis deviation, and certain changes of rate and rhythm. While a large percentage of apparently normal senile hearts have a normal tracing, about one-fourth present evidence of important abnormalities indicating myocardial damage.

MAXWELL

Flack, H. A., Mart, J. R., and Maher, C. C.: A Study of the Serial Electrocardiographic Pattern Changes Occurring with Two Sequential Anterior Myocardial Infarctions. Am. J. M. Sc. **228:** 288 (Sept.) 1954.

The authors have made a clinical and serial electrocardiographic study of 12 patients who had experienced 2 sequential myocardial infarctions, anterior in location. Two of the patients were examined at necropsy. It was emphasized that a second anterior infarction following the first anterior lesion produced conventional changes in the serial electrocardiographic tracings. The serial changes resulting from the second infarction were not obscured by the

residual defects of the first infarction remaining in the electrocardiogram. In order to make a diagnosis of the second anterior infarction, it is necessary to observe serial electrocardiographic changes and to have available the clinical and electrocardiographic records of the first infarction. The serial tracings are essential for determining the existence of the old and new lesions. Residual defects in the electrocardiograms were more marked after the second than after the first infarction. It is suggested that second myocardial infarctions in the same area occur much more frequently than recognized.

SHUMAN

ELECTROKYMOGRAPHY

Blumberger, K. J., Brommer, W., Meiners, S., and Walz, L.: Electrokymographic Studies in Alternans of the Heart. Ztschr. Kreislaufforsch. **431:** 521 (August) 1954.

In two patients with pulsus alternans electrokymograms were recorded of both ventricles and various portions of the aorta, in part with simultaneous registration of the sphygmogram of the carotid artery or pressure curves of the right ventricle and pulmonary artery. The analysis of the data revealed that the variations in aortic pulsations parallel those of the peripheral pulse. In ventricular kymograms the difference between larger and smaller systoles is revealed by different inclination of the systolic component. This alteration is however not always equally pronounced in the two ventricles. In one of the patients paradoxical pulsations were found of the entire left ventricular border varying in extent with the degree of pressure differences between the two types of systoles.

All these findings are interpreted to provide support of the views that pulsus alternans in man is caused primarily by a disorder of contractility of the heart rather than by a disturbance of hemodynamics.

PICK

ENDOCRINE EFFECTS ON CIRCULATION

Peschel, E., and Race, G. J.: Studies on the Adrenal Zona Glomerulosa of Hypertensive Patients and Rats. With Special Reference to the Effect of Dietary Salt Restriction. Am. J. Med. **17:** 355 (Sept.) 1954.

Comparison of the zona glomerulosa of the adrenals of 54 hypertensive patients who died while on the salt-free rice diet with that of 20 patients who died suddenly without preceding illness, with 13 hypertensive patients on a normal diet, and with 15 malnourished cancer patients, indicates that the width of the zona glomerulosa of the patients on the rice diet was increased significantly in 24 per cent, within normal range in 70 per cent, and insignificantly below the normal range in 6 per cent. Hypertensive rats on a salt-free diet showed a similar marked increase in the width of the zona glomerulosa in comparison to hypertensive rats on diets with normal salt content. Similarly, normal rats on a salt-free diet compared to normal rats on a normal diet showed a marked increase in width of the zona glomerulosa.

The cytoplasmic fat content was decreased in the human adrenals when the width of the zona glomerulosa was greater than normal and was the same as in the controls when the width was in the normal range. Special histochemical staining technics identified the cytoplasmic fat as ketosteroid in type.

The increased width and decreased fat content of the zona glomerulosa are interpreted as evidence of increased hormone production without storage. It is suggested that this may be due to the decreased sodium-potassium ratio which stimulates the production of electrolyte-regulating corticoids. In regard to the influence of the rice diet on the adrenal cortex, definite cortical atrophy, such as would indicate reduced cortical activity, was not observed in a single instance. No conclusions can be drawn regarding the role of the adrenal cortex in the genesis of hypertension.

HARRIS

Williams, C. D., Herple, K. G., and Ebert, R. H.: The Effect of Cortisone on Vascular Reactivity: In Vivo Observations Using the Rabbit Ear Chamber Technique. J. Lab. & Clin. Med. **44:** 210 (August) 1954.

Using the rabbit ear chamber technique, measurements were made on the constriction in arterioles caused by nor-epinephrine and histamine in normal and cortisone treated animals. The experiments were well controlled. There was no effect produced by cortisone upon the vasoconstriction brought about by nor-epinephrine or histamine on the arterioles.

HARVEY

Adlersberg, D., Schaefer, L. E., and Wang, C-I.: Adrenal Cortex, Lipid Metabolism, and Atherosclerosis; Experimental Studies in the Rabbit. Science **120:** 319 (Aug. 20) 1954.

The combination of cortisone or hydrocortisone administration, in addition to cholesterol feeding, in rabbits, results in a considerable elevation of plasma lipid fractions—definitely higher than those seen on cholesterol feeding alone. Discontinuation of corticosteroid administration but continuation of cholesterol feeding resulted in a return of the lipid level to that of cholesterol feeding alone. Corticotropin (ACTH) was less effective than the steroids.

Atherogenesis and the deposition of cholesterol in other tissues was inhibited by this combination in spite of the extreme hypercholesterolemia. The authors suggest that corticosteroids diminish tissue permeability of lipids.

WAIFE

HYPERTENSION

Kubicek, W. G., Kottke, F. J., Laker, D. J., and Visscher, M. B.: Vasomotor Nerve Stimulation and Mechanical Obstructive Factors in Renal Hypertension. Am. J. Physiol. **178:** 246 (August) 1954.

As long as renal function remained adequate as judged by endogenous blood creatinine (and presumably blood urea) chronic stimulation of renal arteries and associated nerves or of the splanchnic nerves caused a hypertension for the duration of the application of the stimulus. Decrease in renal circulation prevented the onset of hypertension due to stimulation. In one dog with renal arteries completely occluded an extensive collateral circulation maintained normal clearance values. Four periods of stimulation produced a hypertension which persisted after stimulation stopped. A change in renal blood supply was implicated in this case.

OPPENHEIMER

Tobian, L., Jr., and Binion, J.: Effect of Deficiency of Renal Tissue With or Without Resulting Hypertension on the Electrolyte Composition of Brain and Skeletal Muscle. Am. J. Physiol. **178:** 233 (August) 1954.

When one kidney is removed and the other compressed with a figure of eight ligature in rats some become hypertensive, but others remain normotensive. Potassium of operated normotensives is increased in brain and muscle although intracellular sodium of muscle is decreased and sodium content of brain is increased when compared to unoperated controls. These changes were present whether or not there was renal insufficiency with increased blood urea nitrogen. The only difference observed in operated hypertensive rats was a significant 2% decrease in brain potassium.

OPPENHEIMER

Scebat, L., Kremer, R., Lenègre, J., and Damien, J.: Hemodynamic Study in Hypertensive Heart Disease. Arch. mal. coeur. **8:** 666 (Aug.) 1954.

In 35 cases with hypertensive heart disease in various clinical stages, the hemodynamics including calculations of the work of the right and left ventricle were compared with similar data of cases with valvular and coronary heart disease. In 15 of the patients a vasodepressor (Regitine, Pendiomide or Apresoline) was injected through the cardiac catheter into the pulmonary artery, and the effect recorded upon right ventricular pressure, cardiac output and the work of the heart.

The hemodynamics in the various stages of hypertensive heart disease do not differ from those found in other types of cardiopathies involving the left ventricle, and the alterations parallel the clinical manifestations. Left ventricular work, increased in the initial stage, falls to a certain extent with onset of heart failure but remains elevated as heart failure progresses. The work of the right ventricle, on the other hand, was found to increase progressively in the course of the evolution. Under the effect of vasodepressors the work of the right heart remained unchanged regardless of the stage of the disease, whereas left ventricular work was reduced to varying degrees, most so in well-tolerated hypertension, and least in the presence of heart failure. The significance of these data relative to the various factors which cause, or contribute to, the development of heart failure in hypertensive heart disease is discussed.

PICK

Allen, E. V., Barker, N. W., Hines, E. A., Jr., Kvale, W. F., Shick, R. M., Gifford, R. W., Jr., and Estes, J. E., Jr.: Medical Treatment of Essential Hypertension. Proc. Staff Meeting, Mayo Clinic **29:** 459 (Aug.) 1954.

The authors summarize briefly their experiences and methods of administration of a number of drugs used in the treatment of hypertension. All the more common hypotensive drugs are briefly introduced, mode of administration discussed and the kind of response to be anticipated covered. This presentation is not concerned with the results of treatment carried out over periods of several months.

As in all methods of medical treatment of hypertension, the proof of effectiveness can be determined only by trial. Predictability of effectiveness of a program of treatment is of a very low order; the physician may need to try various combinations of drugs in varying doses until a satisfactory program is achieved.

They believe that physicians should approach the problem of medical treatment of essential hypertension with optimism, for this attitude coupled with information and skill produces gratifying results on many occasions. One need only recall the intense and prolonged effort devoted to the care of patients with such conditions as leukemia, malignancy and tuberculosis to justify the same devotion to the care of patients with essential hypertension.

SIMON

Counihan, T. B., and Doniack, I.: Malignant Hypertension Supervening Rapidly on Pre-eclampsia. J. Obst. & Gynaec. Brit. Emp. **61:** 449 (August) 1954.

Two rare cases of pre-eclampsia are reported in detail. Both patients had pre-eclampsia and after delivery showed an extremely unusual course in that they progressed rapidly with evidences of malignant hypertension into uremia and death. Acute idiopathic hemolytic anemia also occurred in both patients. At autopsy, the kidneys of each patient were found to show the characteristic changes of malignant nephrosclerosis. The cause of the malignant course in these two individuals was not indicated.

It was not related to prolonged toxemia since both were toxemic for only a short period.

SAGALL

Govan, A. D. T., and MacGillivray, I.: Renal Function and Chloride Metabolism in Pre-eclamptic Toxemia. J. Obst. & Gynaec. Brit. Emp. **61:** 491 (August) 1954.

A short salt-loading test was performed on a series of women in the child-bearing age. Eight of the pregnant patients had developed pre-eclamptic toxemia and four more had hypertensive disease with some degree of renal failure. Three normal pregnant patients and two non-pregnant subjects were used as controls.

The delayed excretion of injected chloride found in the non-pregnant subjects was increased by pregnancy and much more so when pre-eclampsia was present. In pregnancy complicated by hypertensive disease and renal deficiencies, the rate of chloride excretion, however, was increased and exceeded that of the normal non-pregnant individual. Analysis of the results indicates that in normal pregnancy there is increased tubular re-absorption of chloride. With renal disease the increased output of chloride is related to the structural damage that has occurred. In pre-eclampsia, the diminished output of injected chloride is explained as being due to a functional change, differing from the normal only by degree. The authors believe that the increased re-absorptive capacity of the renal tubules for chloride in the pregnant state, both normal and pre-eclamptic, is related to adrenal action.

SAGALL

Finnerty, F. A., Jr.: The Use of 1-hydrazinophthalazine (Apresoline) in the Management of Hypertension Appearing Early in Pregnancy. Am. J. M. Sc. **228:** 140 (Aug.) 1954.

A group of patients with hypertension observed in pregnancy received Apresoline in gradually ascending doses from 40 mg. per day to 400 mg. per day or until the limits of tolerance were reached. In 10 patients, the dosage was increased further to 800 mg. per day. Of the 91 patients, 44 had hypertensive vascular disease, 29 had hypertension plus toxemia, and 18 had true toxemia. The importance of the ophthalmoscopic examination in the recognition of toxemia and the differentiation of this condition from hypertensive disease is stressed. The average effective dosage was found to range from 200 to 300 mg. per day. The incidence of toxicity increased at higher dosage levels without producing favorable therapeutic effects. Based on the blood pressure responses, there were 36 excellent, 9 good, 6 fair, and 40 poor results. Headache was the predominant toxic manifestation occurring in 34 patients; flushing of the face, dizziness, anxiety and drowsiness were also observed. The favorable response noted in 1 out of every 3 patients treated suggests that Apresoline should be administered in patients with early toxemia or progressive hypertension during pregnancy. Hospitalization is recommended if the toxemia process is not controlled within two weeks with this drug.

SHUMAN

Feder, I. A.: Febrile Syndrome During Prolonged Hydralazine Treatment for Hypertension. New Eng. J. Med. **251:** 273–274 (Aug. 12) 1954.

The author describes a man, aged 40 years, with malignant hypertension who was treated with Hydralazine hydrochloride (Apresoline) for more than one year with dosages totalling 800 mg. daily for more than 10 months of that period. At the end of this time the patient developed a severe febrile illness associated with migrating pain, reddened elevated lesions of the skin of the legs, anorexia and tachycardia. The clinical picture resembled polyarteritis. Repeated L. E. tests were negative. Symptoms persisted even though the Hydralazine was discontinued. A favorable response followed treatment with ACTH and cortisone.

ROSENBAUM

Kert, M. J., Rosenfeld, S., Mailman, R. H., Westergart, J. P., Carleton, H. G., and Hiscock, E.: Clinical Evaluation of Hydralazine (Apresoline) Alone and in Combination with Veriloid in the Treatment of Hypertension. Angiology **5:** 318 (Aug.) 1954.

Among 43 ambulatory hypertensive patients receiving Apresoline alone for from three to 22 months, 30 per cent had a good and an additional 28 per cent had a fair hypotensive response. When Veriloid was added to Apresoline some of the side effects of the latter drug were alleviated and the hypotensive response was improved to a degree that could not be achieved by either drug alone.

WESSLER

PATHOLOGIC PHYSIOLOGY

Chinard, F. P., and Enns, T.: Transcapillary Pulmonary Exchange of Water in the Dog. Am. J. Physiol. **178:** 197 (August) 1954.

Labeled red cells or Evans blue were injected into a jugular vein and collected at very short intervals from the carotid or brachial arteries. These two were considered as reference substances which remain in the blood stream. When compared to these two substances there is little displacement of the curves representing sodium, para-aminohippurate, thiocyanate, inulin or urea. On the other hand deuterium and tritium oxides were observed to have considerable displacement. There was, however, little over-all loss. The authors consider that this represents passage and return of water through the capillary walls. The rate of this loss is almost equal to the output of the right ventricle. Diffusion, rather than a filtration hypothesis, fit the data.

OPPENHEIMER

Popper, H. L., Jefferson, N. C., Wulkan, E., and Necheles, H.: Liver Function Following Partial Devascularization of the Liver. Am. J. Physiol. **178:** 321 (August) 1954.

In these experiments there was interference with the blood supply of the liver. Despite this there were no important changes in serum cholesterol, cholesterol esters or blood sugar. Degree of devascularization and time elapsed were not factors. Elevation in serum alkaline phosphatase was not proportional to the degree of devascularization. Serum albumin was markedly reduced and the A/G ratio was reversed. These last results are proportional to reduction in hepatic circulation and duration of devascularization was a factor. There was no tendency to bleeding.

OPPENHEIMER

Moore, N. S., Young, C. M., and Maynard, L. A.: Blood Lipid Levels as Influenced by Weight Reduction in Women. Am. J. Med. **17:** 348 (Sept.) 1954.

Blood lipid data on 24 women who lost 15 to 60 pounds in weight, at rates varying from 0.6 to 2 pounds per week, on diets containing 1400 calories with 50–80 grams of fat daily, reveal a rather wide fluctuation which occurs in women whether losing weight under dietary control or changing little in weight without dietary control. Data was also presented for 12 women of comparable age who did not lose weight over a similar period of time.

The data provide no support for the view that weight loss is accompanied by a drop in cholesterol or other blood lipids. On the contrary, a slight rise was indicated for a majority of the subjects. In the case of serum cholesterol and phospholipids, statistical analyses revealed an increase of 0.58 mg. of cholesterol and 0.64 mg. phospholipid per pound of weight loss for the group losing weight; both were significant at the 5 per cent level.

HARRIS

Duomarco, J. L. and Rimini, R.: Energy and Hydraulic Gradients Along Systemic Veins. Am. J. Physiol. **178:** 215 (August) 1954.

Physical models are used in this study to analyze hydraulic and energy gradients in the systemic veins. Records were obtained in dogs simultaneously from various locations in the veins and from either intrathoracic or intra-abdominal locations. The intrathoracic and superior vena cava pressures vary in a parallel manner. The same statement can be made of abdominal inferior vena cava and intra-abdominal pressures. There is a marked change in the hydraulic venous gradient at the point of departure from abdomen into thorax. The central venous pulse is not transmitted beyond the thorax. Respiratory fluctuations are not observed in the jugular vein. The conclusion is expressed that venous return is not directly affected by respiration.

OPPENHEIMER

Hilton, J. G., and Brown, R. V.: Cardiovascular Responses to Nor-Epinephrine Before and After Denervation of the Pressoreceptors. Am. J Physiol. **178:** 211 (August) 1954.

Pressor responses to nor-epinephrine were greater in duration in the presence of intact pressoreceptors. The mean of the pressor responses and that of the peak blood pressures never were as great after pressoreceptor denervation as during the control period when they were intact. It is concluded, in agreement with work on epinephrine, that elevation of blood pressure due to nor-epinephrine is not limited as to rise or as to peak attained by pressoreceptor reflexes. Some of the cardiovascular response seems to be lost after pressoreceptor denervation. In addition, myocardial depression is more marked after nor-epinephrine in the absence of pressoreceptors. Pulses alternans and small pulse pressures are common in this situation, more so than with epinephrine.

OPPENHEIMER

Buchanan, T. J., Walls, E. W., and Williams, E. S.: Studies in Radiosodium Clearance from the Skin in Man. Clin. Sc. **31:** 321 (Aug.) 1954.

In thirty normal subjects Na^{24} clearances were determined from the skin of the forehead and the leg. The rate of clearance from the forehead was found to be always faster than from the leg. Clearance rates from symmetrical areas of the legs were generally almost equal, but in some cases there were distinct differences. The more rapid clearance from the forehead skin suggests that this is due to the greater vascularity of the scalp. A greater capillary surface is available for this clearance and there may be more rapid blood flow through these vessels than in those of the leg. Also there is a higher degree of vasoconstrictor tone in the vessels of the leg. The results appear to support the belief that the rate of clearance is a measure of local circulatory efficiency.

ENSELBERG

Prime, F. J., and Westlake, E. K.: The Respiratory Responses to CO_2 in Emphysema. Clin. Sc. **31:** 321 (Aug.) 1954.

Studies were performed on 35 emphysematous patients and 13 controls in order to determine whether the diminished response to CO_2 in emphysema was due chiefly to diminished sensitivity of the respiratory center. All subjects had respiratory function studies. Their responses to breathing 100% oxygen, and 5–7% CO_2 in oxygen were studied.

In 26 emphysematous patients the inhalation of pure oxygen was followed by a fall in ventilation. This was due to the relief of anoxia and did not occur in the patients with normal oxygen saturation or in the controls. As a result of this fall in ventilation there was a rise in alveolar pCO_2, a corresponding rise in arterial pCO_2, an increase in plasma CO_2 and a fall in blood pH. The rise in ventilation while breathing CO_2 was diminished in the emphysematous

patients. The influence of changes in pCO_2 in these patients was eliminated by measuring their responses to CO_2 under conditions of full oxygenation. The diminished responses could be correlated with the degree of CO_2 retention, being greater with higher levels of resting arterial pCO_2. Although part of the diminished responses is due to an increase in the blood buffering power, the major factor is most probably a reduction in sensitivity of the respiratory center.

ENSELBERG

Kowalski, H. J., Rutstein, D. D., and Reynolds, W. E.: Cardiovascular Studies During Upper Respiratory Tract Infection in Normal Subjects. Am. J. M. Sc. **228:** 275 (Sept.) 1954.

The present study was conducted as the initial step in determining the mechanisms by which upper respiratory tract infections may precipitate congestive failure. The influence of such infections upon salt and water metabolism was examined in 17 normal medical students and compared with the results obtained in the same subjects during a symptom-free period. It was found that the differences between the control and U.R.I. observations in Evans blue space, thiocyanate space and body weight were not statistically significant. Similarly no differences were observed in the hematocrit, red cell count, hemoglobin, serum sodium, potassium, chloride, creatinine and freezing point depression during the two periods. The average change in total serum protein was an increase of 0.3 gm. per cent. The urine studies reveal no significant change in volume, specific gravity, or solute concentration. Thus, there were no alterations in salt and water metabolism found in normal subjects following the onset of minor respiratory tract infections which might explain the occurrence of congestive failure in cardiac patients under similar conditions.

SHUMAN

Kremer, R., Scebat, L., Lenègre, J., and Damien, J.: A Hemodynamic Study in Left Cardiopathies with Exclusion of Mitral Disease. I, Arch. mal. coeur. **47:** 654 (Aug.) 1954.

90 patients with various types of cardiac pathology involving the left ventricle, mitral regurgitation excluded, were submitted to hemodynamic studies. A certain relationship was found between various clinical stages and the hemodynamic alterations. Thus in the course of the evolution of the disease, the cardiac index, initially normal, tends to decrease progressively whereas the pulmonary capillary pressure rises. The left auricular pressure, on the other hand, does not change even in the terminal stages of the disease. None of these three factors is by itself characteristic for a certain stage but in association they provide information considering the phase of evolution. Sometimes, however, it may be necessary to resort to an exercise test in order to demonstrate the alterations of hemodynamics which may be normal at rest even in advanced stages of the disease. Treatment of existent heart failure may reduce the elevated pulmonary capillary pressure to normal or subnormal values at any stage. This does not occur when heart failure is due to mitral insufficiency.

PICK

PATHOLOGY

Brandenburg, R. O., Edwards, J. E.: Cardiac Clinics. CXLIII. Cardiac Sarcoma: Report of Case and Comparison with a Case of Metastatic Carcinoma of the Pericardium. Proc. Staff Meet. Mayo Clinic **29:** 437 (Aug.) 1954.

It is the purpose of this paper to report a case of cardiac sarcoma in which the ante-mortem diagnosis was not made but considered, and a case of hemopericardium secondary to carcinoma of the lung in which the ante-mortem diagnosis was made.

In case 1, the nature of the tumor was that of a sarcoma. The presence of the large mass in the wall of the right atrium suggested that the tumor originated at this site and involved the pericardium secondarily. The clinical picture was that of cardiac failure without obvious cause. An interesting feature was the roentgenographic and roentgenoscopic demonstration of prominence of the cardiac silhouette in the area in which a large left atrium commonly is noted in cases of mitral stenosis. More attention probably should have been given to this finding since at roentgenoscopy the prominence did not seem to be the left atrium.

In case 2, the hemorrhagic pericardial effusion resulting from metastasis of a tumor of the lung produced cardiac signs and symptoms which caused the patient to seek medical aid. Such an occurrence is unusual, since in cases of metastatic carcinoma of the pericardium it ordinarily is the primary tumor or extracardiac metastasis that produces symptoms and causes the patient to seek medical aid. Metastatic tumors of the heart usually produce few if any symptoms.

In the 2 cases reported in this paper, the common feature was the presence of pericarditis as evidenced by a transient friction rub, pericardial effusion, paradoxical pulse, and eventual cardiac tamponade. In the second case, the clinical diagnosis was confirmed by the finding of carcinoma cells in the pericardial fluid.

SIMON

PHARMACOLOGY

Reinhardt, D. J., and Waldron, J. M.: Lupus Erythematosus-like Syndrome Complicating Hydralazine (Apresoline) Therapy. J.A.M.A. **155:** 1491 (Aug. 21) 1954.

Prolonged therapy with large doses of Hydralazine has been reported to produce a syndrome which progresses from mild arthralgia to a clinical picture of rheumatoid arthritis and finally to a simulation of

disseminated lupus erythematosus. A patient is reported in whom there was a reaction to Hydralazine exhibiting not only the clinical picture of rheumatoid arthritis and disseminated lupus erythematosus but also the pathological evidences of these diseases in the form of a rheumatoid nodule and acute collagenous necrosis of the skin.

KITCHELL

Shackman, N. H., Swiller, A. I., and Morrison, M.: Syndrome Simulating Acute Disseminated Lupus Erythematosus. J.A.M.A. **155:** 1492 (Aug. 21) 1954.

Previous reports have appeared in the literature implicating large doses of Hydralazine over long periods of time with the syndrome consisting of rheumatic manifestations varying from fleeting mild arthralgias to full blown arthritis and followed in a few patients by a clinical picture that showed remarkable resemblance to acute disseminated lupus erythematosus. In this case a clinical and laboratory picture mimicking acute disseminated lupus erythematosus developed in a woman after therapy with moderate doses of Hydralazine over a period of 9 months. There was complete regression of all clinical signs and symptoms and all laboratory findings within one month of the discontinuance of therapy with the drug.

KITCHELL

Weinstein, L., Goldfield, M., and Chang, T.: Infections During Chemotherapy. A Study of Their Frequency, Type and Predisposing Factors. New Eng. J. Med. **251:** 247–255 (Aug. 12) 1954.

Superinfection is a by-product of chemotherapy which occurs when the normal bacterial population is altered by treatment of a patient with an infectious disease so that a serious infection is superimposed upon that one for which treatment was begun initially. This study is based upon observations made in 3095 patients who received one or more antibiotic agents. Patients who received one of the sulfonamides alone were not included in this report. There were 68 superinfections in this group of patients, an incidence of 2.19 per cent. Superinfections after penicillin treatment were apt to be due to gram-negative bacteria. Staphylococcus aureus infections tended to complicate penicillin or streptomycin therapy. In many instances the relative insensibility of the organism causing the superinfection was so great as to make its treatment much more difficult than the primary infection. In a few instances the secondary infection proved untreatable and fatal. The superinfection often involved the same organ as the initial infection. Regardless of the location of the first infection, the secondary involvement almost always involved the respiratory tract. The lower the involvement of the respiratory tract, the greater the incidence of superinfection was found to be. Superinfection occurred in 20 per cent of the cases of pertussis. Superinfection was more common with antibiotics or combinations of drugs having a broad antibacterial effect. Complicating infections were more common in patients three years of age or less. Most of the superinfections occurred between the third and sixth days of treatment of the primary disease. It is emphasized that secondary bacterial infections may occur despite the use of chemotherapy and that it is impossible to establish such infections specifically without bacteriologic study. The appearance of superinfection during the administration of an antibiotic may convert a benign, self-limited disease into a serious, prolonged or even fatal illness.

ROSENBAUM

Cardillo, T. E., Mullin, E. W., Schiffer, L. M., and Lyons, R. H.: Satisfactory Use of a Carbonic Anhydrase Inhibitor as an Oral Diuretic. Am. J. M. Sc. **228:** 214 (Aug.) 1954.

The inhibition of the enzyme, carbonic anhydrase, in the renal tubular cells reduces the availability of hydrogen ions within the tubular epithelium for exchange with the sodium ions of the glomerular filtrate in the lumen of the tubule. This sodium is excreted together with potassium ions which normally compete with hydrogen ions for excretion via the same tubular mechanism. The effectiveness of Diamox in producing diuresis was evaluated by means of determining the body weights of 25 patients in congestive heart failure requiring diuretics. The mean weight loss of the group per 48 hours was observed during the administration of Diamox and Thiomerin given at different intervals. The weight loss response to Thiomerin was found to increase in direct linear relationship to increasing doses of the drug. The majority of the patients lost less than two pounds per 48 hour period on Thiomerin. On the other hand, Diamox administration gave a uniform response in weight loss above the 250 mg. dosage and the majority of the patients lost more than 2 pounds per 48 hour period with this drug. It was shown to possess a high degree of diuretic potency with minimal systemic toxicity consisting of transient mild paresthesias of fingers and toes of 3 out of the 25 patients.

SHUMAN

Feinberg, H., Rubin, L., Hill, R., Entenman, C., and Chaikoff, I. L.: Reduction of Serum Lipids and Lipoproteins by Ethionine Feeding in the Dog. Science **120:** 317 (Aug. 20) 1954.

Ethionine, the ethyl analogue of methionine, can induce fatty livers in rats. When dogs are fed 125 mg. of *dl*-ethionine daily there is a prompt reduction in the level of serum fatty acids, phospholipids, and cholesterol. (The serum cholesterol fell from 180 to 20 mg. per 100 ml. serum.)

Ethionine also caused a marked reduction in the level of low- and high-density lipoproteins. Removal

of ethionine from the diet resulted in a prompt restoration of all lipid and lipoprotein fractions to normal levels.

WAIFE

Moyer, J. H., and Morris, G.: Cerebral Hemodynamics During Controlled Hypotension Induced by the Continuous Infusion of Ganglionic Blocking Agents (Hexamethonium, Pendiomide and Arfonad). J. Clin. Invest. **33:** 1081 (Aug.) 1954.

During controlled hypotension (induced by the continuous infusion of Hexamethonium, Pendiomide or Arfonad), the cerebral blood flow was decreased in 17 of 19 subjects. With the decrease in blood flow more oxygen was extracted from the blood by the brain. At low levels of blood pressure (under 60 mm. Hg) this compensation was at times inadequate and symptoms of cerebral hypoxia developed. The cerebral blood flow increased when the blood pressure was raised by vasopressor drugs.

WAIFE

Cooke, R. E., Segar, W. E., Reed, C., Etzwiler, D. D., Vita, M., Brusilow, S., and Darrow, D. C.: The Role of Potassium in the Prevention of Alkalosis. Am. J. Med. **17:** 180 (Aug.) 1954.

Loads of sodium bicarbonate administered to normal rats in drinking water along with known amounts of potassium and chloride did not produce alkalosis after two weeks as long as potassium chloride intake exceeded 0.5 mM/kg./day even though sodium bicarbonate intake amounted to 10–30 mM/kg./day. Alkalosis could not be produced in this way in the absence of potassium deficiency, as demonstrated by muscle analysis.

Other rat experiments suggest that citrate may be substituted for chloride in the renal defense against alkalosis so that sodium is excreted without chloride and without change in urinary pH. Potassium appears essential for the maximal conservation of chloride in this way.

The authors' results suggest that potassium deficiency may alter the ratio in which sodium and chloride are reabsorbed from the glomerular filtrate. Such an alteration leads to changes not only in extracellular concentration but also in extracellular volume.

HARRIS

McCabe, E. S, and Wilson, W. W.: Dangerous Cardiac Effects of Tetraethylthiuram Disulfide (Antabuse) Therapy In Alcoholism. Arch. Int. Med. **94:** 259 (Aug.) 1954.

Each patient prior to the institution of Tetraethylthiuram disulfide (Antabuse) therapy should be exhaustively studied from a cardiac standpoint. Thirty-five per cent of the patients in the present series showed evidence of dangerous cardiac embarrassment in alcohol-Tetraethylthiuram disulfide testing, despite negative cardiac history and absence of abnormal clinical findings. Special consideration, therefore, should be given to this group of patients as regards continuation of Tetraethylthiuram disulfide therapy.

BERNSTEIN

Van Goidsenhoven, G.M.-T., Gray, O. V., Price, A. V., and Sanderson, P. H.: The Effect of Prolonged Administration of Large Doses of Sodium Bicarbonate in Man. Clin. Sc. **31:** 383 (Aug.) 1954.

Studies were performed on 33 patients with peptic ulcer who were being treated with a milk drip containing large amounts of sodium bicarbonate. Doses up to 145 gms. daily were well tolerated for as long as three weeks. All patients developed alkalosis with a rise in plasma CO_2 and blood pH, but adverse symptoms were few and trivial. Renal function studies showed an increase in glomerular filtration. Plasma sodium rose in most cases, balance studies indicating retention of large amounts of sodium. Most of the sodium appears to be accomodated in a greatly expanded extracellular space, and there is probably a shift of chloride from cells to extracellular fluid as bicarbonate is exchanged.

It would appear that alkalosis per se rarely causes renal damage and that the renal failure seen in the clinical alkalosis results primarily from dehydration or hemorrhage. The renal failure is of ischemic origin and not a direct consequence of alkalosis. Although the authors have shown that large doses of alkali can be easily handled by patients with good renal and cardiac function, they stress the need for close clinical and biochemical supervision of the treatment, preferably in a hospital.

ENSELBERG

Kistner, R. W.: Treatment of the Acute Toxemias of Pregnancy with Hypotensive Drugs. J. of Obst. & Gynaec. Brit. Emp. **61:** 463 (Aug.) 1954.

The author studied the effects of hypotensive drugs in a series of 77 patients. Of these 53 were suffering with pre-eclampsia, 2 with eclampsia, 15 with essential hypertension with superimposed pre-eclampsia and 7 with essential hypertension. Of this series 29 received no treatment and served as controls. During the period of testing all the patients were hospitalized and placed on a low-sodium diet.

Three drugs were studied separately and in conjunction with each other. Veratrone was given intravenously to 18 patients. The rate of flow was adjusted depending upon the resulting degree of hypotension and bradycardia. After 24 to 48 hours of intravenous therapy, the subcutaneous route of administration was employed with injections at two hourly intervals to maintain the blood pressure at approximately 140/90 and the pulse at 80. Verenteral, a purified alkaloid of Veratrum Viride, was employed in 10 patients. Initially, the drug was given rapidly intravenously and then followed by

slow continuous intravenous. Apresoline was given intravenously to 20 patients. It was administered every 6 to 8 hours depending upon the degree of hypotension. The most severe pre-eclamptic patients were selected for treatment with Apresoline. In 14 patients tetro-ethyl ammonium chloride was used as a testing agent to determine the degree of neurogenic and non-neurogenic hypertension.

In acute toxemia, Veratrone produced a constant hypotension and bradycardia. This was usually associated with nausea and vomiting. During the period of maximum hypotension the urinary output was temporarily reduced.

Similar results were obtained with Verenteral. In four cases, however, ventricular extrasystoles were induced by this drug.

Apresoline in acute toxemia resulted in a marked hypotension and tachycardia. Headache was observed in 32 per cent of the patients. There was no suppression of urinary output. Clinical improvement, both subjective and objective, was observed routinely following Apresoline administration.

The author concludes that the hypotensive drugs offer a physiologic mechanism for the release of the vasospasm associated with the acute toxemias and that Apresoline has simplified the treatment of toxemia. Drugs of this nature offer definite promise in these cases and further investigative work is indicated.

SAGALL

Moyer, J. H., and Handley, C. A.: Blood Pressure and Renal Hemodynamic Responses to Aramine and the Alterations of These Responses by Adrenergic Blockade with Dibenzyline. Am. Heart J. **48:** 173 (Aug.) 1954.

Observations were made on the acute renal hemodynamic response to a continuous intravenous infusion of Aramine, a synthetic sympathomimetic amine, in dogs. As the blood pressure increased, renal vasoconstriction occurred and renal blood flow was depressed. When renal vasoconstriction became marked, glomerular filtration was also depressed. The renal excretion of water and electrolytes was not altered in any consistent fashion unless glomerular filtration rate was markedly reduced. When this occurred, the excretion rates of water and sodium were depressed.

The blood pressure and renal hemodynamic response to a continuous infusion of Aramine were completely blocked by the antecedent administration of Dibenzyline, thus suggesting that the renal vasoconstrictive response to adrenergic drugs is blocked by adrenergic blockade.

MAXWELL

Lieberman, A. L., Schwartz, S. S., and Cooper, M.: Evaluation of Intravenous and Oral Use of Metrazol in Hospitalized Arteriosclerotic Psychiatric Patients. Geriatrics **9:** 371 (Aug.) 1954.

A series of 41 hospitalized psychiatric patients with arteriosclerotic changes was utilized to evaluate the effects of intravenous and oral Metrazol. A group of 17 was given the drug intravenously, a group of 11 received the drug orally, while a third control group of 13 received placebo medication. The entire group of patients was assumed to be approximately stabilized arteriosclerotics; the majority were classified as having chronic brain syndrome with associated or dissociated psychiatric disorders. Based on clinical impression, one-third of the intravenous group and about one-half of the oral group improved significantly, and about one-fourth of the control group showed changes suggesting improvement. The general clinical impression of improvement was not borne out by psychologic tests, which failed to show statistically significant differences in the 3 groups.

MAXWELL

PHYSICAL SIGNS

Stembridge, V. A., Hejtmancik, M. R., and Herrmann, G. R.: Unusual Musical Murmurs of Anterior Cusp Aortic Regurgitation. Report of Ten Cases. Am. Heart J. **48:** 163 (Aug.) 1954.

Ten patients with musical aortic diastolic murmurs were observed during a 12-year period. All occurred in Negro males and were of syphilitic etiology. An analysis of the authors' series combined with previous reports showed that the vast majority were due to syphilis, the remainder being associated with rheumatic aortic valvulitis, bacterial endocarditis, or traumatic rupture. The right anterior aortic cusp is by far the most often involved, usually with eversion of the cusp. Appearance of the murmur was generally followed by marked adverse change in the circulatory status and gravely altered the prognosis; nine of the patients died within 9 months, and the remaining one lived 18 months. It was felt that the appearance of a musical aortic diastolic murmur is an ominous prognostic sign, usually indicative of eversion of the right anterior aortic cusp.

MAXWELL

PHYSIOLOGY

Brecht, K., and Boucke, H.: A Method for Continuous Bloodless Registration of the Blood Pressure in Man. Klin. Wochnschr. **32:** 683 (Aug.) 1954.

A new method is described for bloodless continuous registration of the heart rate, systolic and diastolic pressures, pulse amplitude and respiration. The principle consists of amplification of deflections in an infra-sound pulse recorder described previously by the authors. In practice, two such instruments, attached to an extremity, proximal and distal to an ordinary blood pressure cuff, are necessary to follow the alterations in peripheral circulation. The details and the handling of the complex apparatus are described and illustrated by an example of an actual record in a hypertensive patient.

PICK

Weiss, A. J.: Determination of Blood Pressure at the Ankle. J.A.M.A. **155:** 1332 (Aug. 7) 1954.

A method of determining the systolic blood pressure by palpation over the dorsalis pedis with the sphygmomanometer cuff above the ankle is described. This is a useful simple screening test in recognition of coarctation of the aorta and may have value in the study of peripheral vascular disease.

KITCHELL

Björk, V. O., Blakemore, W. S., and Malmström, G.: Left Ventricular Pressure Measurement in Man. A New Method. Am. Heart J. **48:** 197 (Aug.) 1954.

A new technique was described for measuring the left ventricular pressure curve in the unanesthetized man. In the method reported, a needle was first introduced through the posterior chest wall into the left atrium and a small plastic catheter then threaded through the needle via the left atrium into the left ventricle. One case report and several tracings were presented from 28 patients in whom the procedure was successfully performed. The detailed techniques, dangers and limitations were described.

MAXWELL

Hauch, H. J., and Daneel, K. T.: Comparative Determinations of Cardiac Output According to Fick's Method and the Physical Method of Broemser-Ranke. Klin. Wochnschr. **32:** 687 (Aug.) 1954.

In 32 patients, submitted to cardiac catheterization mostly because of mitral disease, determinations of cardiac output according to Fick's formula were compared with values obtained by the physical analysis according to Broemser-Ranke. The study revealed that due to excitement caused by the procedure of catheterization, determinations by Fick's method yield almost regularly too high results. The same difference of 25 per cent was found consistently in output determinations by the other method, as well as in comparative measurements of heart rate and O_2 consumption, performed before and after cardiac catheterization. The sources of error involved in the Fick method are discussed and the possibilities of recognizing elements of the variable factor of excitement are pointed out.

PICK

ROENTGENOLOGY

Fleischner, F. G. and Reiner, L.: Linear X-Ray Shadows in Acquired Pulmonary Hemosiderosis and Congestion, New England J. Med. **250:** 900 (May 21), 1954.

The authors are concerned with the thin horizontal linear shadows which occur in the lateral lower lung field of thoracic roentgenograms taken of patients with acute or chronic pulmonary congestion, primarily patients with mitral valvular disease. These shadows are perpendicular to the lateral chest wall, parallel to each other, spaced 0.5 to 1.0 cm. apart, ranging in thickness from mere visibility to a width of 0.1 to 0.2 cm. and extending into the lung fields no more than 1 to 3 cm. When persistent, the shadows are believed to be due to hemosiderin preferentially appearing alongside and within interlobular septums and are felt to be more frequently seen than the generalized nodularity of far-advanced acquired pulmonary hemosiderosis. When transient and associated with acute pulmonary congestion, the shadows are considered due to widening of the interlobular septums by edema fluid.

Similar shadows in occasional cases of pneumoconiosis and diffuse pulmonary fibrosis are believed due to fibrous thickening of the interlobular septums. These shadows are differentiated from plate-shaped areas of atalectasis which are usually thicker and extend more deeply into the lung. Intrapulmonary scars of infarcts or interstitial extensions of pleurisy are coarser and usually accompanied by visible pleural thickening.

ROSENBAUM

RHEUMATIC FEVER

Diehl, A. M., Hamilton, T. R., Keeling, I. C., and May, J. S.: Long-acting Repository Penicillin in Prophylaxis of Recurrent Rheumatic Fever. J.A.M.A. **155:** 1466 (Aug. 21) 1954.

Ninety-six individuals who had previously had or did have active rheumatic fever and whose ages ranged from 5–20 years were maintained for as long as 14 months with an injection of benzathine penicillin G (Bicillin) 1,200,000 units administered every 4 weeks intramuscularly. During this period of prophylaxis, 1,045 cultures were taken. Although 40 cases showed the presence of beta hemolytic streptococci, only 4 were found to be of the Lancefield group A type. In outpatients with inactive rheumatic fever who were given benzathine penicillin for 7 months, there was only one positive culture that proved to be of Lancefield group A, and there were no group A streptococci found during January, February, or March of 1954. No clinical recurrences of rheumatic fever were observed in patients whose rheumatic activity was quiescent when prophylaxis was instituted. The difficulties inherent in oral medication are that the patient may, or may not, take the dose. The introduction of benzathine penicillin into the medical armamentarium offers a physician an agent that may prove most effective in maintaining an individual patient under observation and management by monthly injections. A program of continuous prophylaxis to stave off intercurrent streptococcic disease appears thus far to be the best available method for the prevention of recurrent attacks of rheumatic fever.

KITCHELL

Stolzer, B. L., Houser, H. B., Clark, E. J.: Comparative Effects of Aspirin, ACTH and Cortisone on the Antistreptolysin "O" Titer and Gamma Globulin Concentration in Rheumatic Fever. J. Lab. & Clin. Med. **44:** 229 (August) 1954.

A study was made on 144 young male rheumatics upon the effects of ACTH, cortisone, and aspirin on the antistreptolysin "O" titer and the gamma globulin concentration in serum during activity of the disease process. Treatment was carried out for six weeks. Signs of hyperadrenalism appeared in those treated with ACTH, but not in those treated with cortisone. Infection was eradicated in every individual by penicillin treatment for two weeks followed by daily sulfadiazine administration during the remainder of the study period. Antistreptolysin "O" titer fell most rapidly in ACTH treated patients. The decrease seen in cortisone and aspirin treated patients was statistically not different from the other, but it was definitely less rapid than in the ACTH treated individuals. Precisely the same effects were seen on gamma globulin concentration in the serum following these three therapeutic agents.

HARVEY

Davis F. W., Jr., and Andrus, E. C.: Mitral Stenosis in Facsimile. New England J. Med. **251:** 297–302 (Aug. 19) 1954.

Three cases are described in detail in which the diagnosis of rheumatic mitral stenosis was made prior to operation or ante-mortem. In one patient a myxoma of the left auricle was found. Although it was separated from the left atrium, attempts to deliver it into the pulmonary vein failed and it was fractured during removal from the left ventricle with embolization and death. In the second case there was a congenital anomaly of the myocardium of the left auricle which produced functional stenosis of the outflow tract of the left ventricle. In the third case collagenous mediastinal thickening constricted the pulmonary veins and produced inflow obstruction into the left atrium.

The clinical entities which may simulate mitral stenosis are described briefly. It is pointed out that intracardiac tumor should be suspected when the murmur is inconstant or variable, the response to digitalis early in the clinical course is poor, there is no history of rheumatic fever, the progression of congestive failure is rapid, there is severe dyspnea and precordial pain in episodes, and the murmurs or clinical status are altered by changes in position. The authors emphasize the importance of awareness of conditions imitating mitral valvular disease in the selection of patients for commissurotomy. When such procedures are undertaken facilities should also be available for removal of tumor, pericardectomy, correction of a congenital anomaly or other surgical procedures for these confusing disorders.

ROSENBAUM

SURGERY

Mahorner, H., and Spencer, R.: Arterial Grafts: A Technique for Replacing Segments of Large Vessels. Angiology **5:** 294 (Aug.) 1954.

Because the thoracic aorta and aortic arch cannot be occluded for prolonged periods without the danger of producing spinal cord ischemia and paraplegia, the authors developed, in dogs, a new and simpler technique for keeping the blood circulating through the aorta while a graft was being inserted. A homologous graft shunt was sutured in place with two end-to-side anastomoses while the recipient aorta was only partially occluded at two levels with Potts and Beck aorta clamps. None of the dogs developed paraplegia although during the time of partial occlusion it was estimated that from 50 to 66 per cent of the lumen of the thoracic aorta was obstructed by the clamps. The authors believe that this method is superior to the use of temporary polyethylene shunts. In one patient the method was successfully employed in inserting a graft and removing a large innominate artery aneurysm.

WESSLER

Hobman, C. W. and Steinberg, I.: Treatment of Superior Vena Caval Occlusion by Arterial Graft. J.A.M.A. **155:** 1403 (Aug. 14) 1954.

A case of superior vena caval obstruction, probably due to a nonspecific mediastenitis was treated by re-establishing circulation with an arterial graft chosen from the blood vessel bank. This graft was an adult descending aorta of ideal length and size. The period of observation following this operation is ten months at present. The authors recommend the use of preserved aortic grafts for the relief of superior vena caval obstruction because of desperate plight of patients with such conditions.

KITCHELL

Soloff, L. A. and Zatuchni, J.: Cardiac Enlargement Following Mitral Commissurotomy. Am. J. M. Sc. **228:** 57 (July), 1954.

The authors report on serial roentgenographic studies made on 44 consecutive patients subjected to mitral commissurotomy. Of the 44 patients, 7 died and 17 could not be adequately followed. Of the remaining 20, chest roentgenograms were obtained over periods ranging from 6 months to 2 years. Immediately after operation, the cardiac silhouette was found to enlarge moderately to massively in each instance, the enlargement apparently involving all chambers. This feature was prominent in all individuals who died postoperatively. During the serial studies, it was found that 11 patients had larger cardiac silhouettes, 4 were unchanged, and 5 were smaller. There was no evidence that mitral commissurotomy can produce a decrease in the size of that part of the cardiovascular system proximal to the obstruction. The enlarge-

ment of the heart noted in many of these patients was considered to have prognostic significance. Some of the factors operating in this connection are pericardial effusion, surgical production of mitral regurgitation, atrial fibrillation, cardiac failure and rheumatic carditis. The authors believe that the reactivation of rheumatic fever best explains generalized cardiac enlargement seen in these individuals. In rare instances, the surgical production of mitral regurgitation may produce permanent cardiac enlargement. In 5 of the 20 patients, diminution of heart size after commissurotomy was attributed to a natural remission from the preoperative event precipitating heart failure.

SHUMAN

Southworth, J. L. and Dabbs, C. H.: Closure of Large Atrial Septal Defect by the Method of Bjork and Crafoord, J.A.M.A. **155:** 1152 (July 24), 1954.

In the Bjork-Crafoord operation, dissection between the two atria creates a groove between the superior vena cava and the right pulmonary veins and a suture is passed in such a way that when tied it obliterates the defect without encroaching on the vena cava, the coronary sinus, or the tricuspid valve. This operation was successfully used to close a large defect in the heart in a case of cor triloculare biventriculare.

KITCHELL

Ellis, F. H. Jr., Logan, G. B., Pender, J. W. and Kirklin, J. W.: Problems in the Thoracic Surgical Management of Infants and Children. J.A.M.A. **155:** 951 (July 10), 1954.

Surgeons are becoming aware that special techniques and methods of care which differ from those commonly used in the adult are necessary in the younger patient. This paper outlines the special problems and the management the authors have found useful in the infant or child undergoing thoracic surgical procedures. Premedication should be light and the dose should be based on body weight. Atropine may often be omitted. Anesthesia should be conducted carefully to avoid anoxia which the child tolerates poorly. Hyperthermia must be avoided and artificially induced hypothermia has often been found useful in children with cyanotic heart disease. During surgery gentle handling of tissues and careful placement of intercostal tubes is important. In postoperative care close nursing supervision and special medical care with proper equipment is needed. Fluid balances and antibiotic administration must be carefully supervised. An atmosphere with adequate oxygen and a high humidity is needed for proper respiration.

KITCHELL

McArt, B. A., Ramsey, F. B., Tosick, W. A. and Woolling, K. R.: Surgical Reversal of Superior Vena Cava Syndrome. Arch. Surg. **69:** 4, (July), 1954.

The authors reported a case of superior vena cava syndrome in a male which was due to a large intrathoracic adenomatous goiter exerting pressure either on the superior vena cava proper or on both innominate veins. Removal of the tumor caused almost immediate disappearance of symptoms and signs, thus indicating either that the obstruction had not been complete, or, if complete, that thrombotic occlusion had not occurred.

It was pointed out that dilated hilar veins, frequently an integral component of the superior vena cava syndrome, produces a hilar shadow on x-ray which may simulate one caused by a pulmonary neoplasm.

ABRAMSON

Neptune, W. B. and Bailey, C. P.: Mitral Commissurotomy through the Right Thoracic Approach. J. Thoracic Surg. **28:** 15, (July), 1954.

The authors described a technic for performing mitral commissurotomy through a right thoracic approach at the level of the fourth intercostal space. In order to expose the lateral portion of the left atrium, it was necessary to mobilize the superior vena cava. This type of procedure was utilized when there were such associated valvular lesions present as tricuspid stenosis, pulmonary pathology and Lutembacher's syndrome. In this manner, a single operation could be utilized to take care of both conditions, thus decreasing the chance of morbid complications and increasing the rate of survival.

ABRAMSON

Rosenbaum, J. B. and Hansen, D.: Simple Cardiac **Pacemaker and Defibrillator.** J.A.M.A. **155:** 1151 (July 17), 1954.

The authors describe a cardiac stimulator incorporating (1) an inexpensive circuit combining a defibrillator and a pacemaker; (2) portability, simple operation, and easy repair; (3) a rapidly applied electrode system for both medical and surgical emergencies; and (4) safety for both patient and physician.

KITCHELL

Brock, R. C.: Mechanical Principles in the Surgery of Aortic and Mitral Incompetence. Brit. Heart J. **16:** 317, (July), 1954.

Brock believes that present methods of correcting aortic or mitral valve incompetence are unsatisfactory. A plastic valve cannot be trouble free for long. Biologic tissues fail 1) because they transform into solid masses unsuitable for valve function 2) placement is such as to fling the flap through the orifice producing obstruction and 3) the axis stream of regurgitation likewise catches the flap and projects

it through the orifice. Perhaps some method of narrowing the dilated ring may be effective.

"At present, it is difficult to feel justified in advising any patient who is suffering from predominant valve incompetence to submit to an operation for its correction."

SOLOFF

Campbell, M., Deuchar, D. C. and Brock, R.: Results of Pulmonary Valvotomy and Infundibular Resection in 100 Cases of Fallot's Tetralogy. Brit. M. J. **1**: 111, (July 17), 1954.

In this group 45 had infundibular resection only, 37 had valvotomy only, and the remaining 18 required both procedures. The mortality in the valvulotomy group was 11% and in the group with infundibular resection, 18%. However, improvement was greater and more consistent in the latter group. In fact, some patients lost all cyanosis at rest and a few even after exertion. In these arterial oxygen saturation was normal and the right-to-left shunt was found by cardiac catheterization to have been reversed. The authors believe there is no appreciable risk of creating a condition comparable to Eisenmenger complex. Enough pulmonary stenosis remains in most cases to prevent inordinate rise in pulmonary artery pressure.

MCKUSICK

Harston, A. P. B.: Mitral Valvulotomy in Pregnancy with Two Illustrative Cases. J. Obst. and Gynaec. Brit. Emp. **61**: 382 (June), 1954.

In general the object of valvulotomy is to improve the cardiac reserve and exercise tolerance of a patient with mitral stenosis and thus restore the individual to an active life. In the pregnant woman the objects of the procedure are many: (1) to improve the cardiac condition for an easier antenatal and labor period, (2) to shorten puerperal convalescence thus enabling restoration of the mother to her household sooner and in a better condition than would be expected in an untreated case; (3) to diminish the chances of congestive failure during the pregnancy, (4) to offer a procedure which may obviate the necessity of termination of pregnancy and sterilization by reducing the morbidity and risk of pregnancy in these patients, and (5) to improve the immediate as well as the ultimate prognosis. The risks of this operation in pregnant women must also be considered. Although the mortality in general is 7.5 per cent, there is every indication that this will decrease in the future with more experience and better selection of patients. Since any operative procedure in pregnancy entails a risk of inducing abortion or premature labor, the operation should not be performed prior to the third month nor after the 34th week of pregnancy. The risk that anesthesia may cause intrauterine death of the fetus is no greater than that associated with Caesarian section. With these factors in mind the author believes that valvulotomy should be considered as an alternative procedure to termination or sterilization in selected pregnant patients. Therapeutically the patients should be grade II (b) or grade III in severity. The predominate lesion should be mitral stenosis without gross mitral insufficiency or aortic lesions. The myocardium should be healthy and an active rheumatic process must be ruled out. Previous congestive failure in pregnancy or evidences of congestive failure in the present pregnancy favor operation. If on general grounds valvulotomy is indicated, the presence of a pregnancy without obstetric complications should not contraindicate the operation. Two cases in whom successful mitral valvulotomy was performed during pregnancy are presented to illustrate the points discussed above.

SAGALL

Gerbasi, F. S. and Blain, A. III: Surgical Aspects of Dissecting Aortic Aneurysms. Angiology **5**: 282 (June), 1954.

Because the treatment of dissecting aortic aneurysm by conventional conservative methods rarely prolongs life, the authors hypothecate that surgical intervention may be of value. Based on knowledge of the pathogenesis of dissecting aneurysm, several surgical techniques are described for use in patients with dissecting aneurysm. The authors clearly state that there is no experimental or clinical evidence to indicate that these techniques are effective.

WESSLER

Lockhead, R. P., Coakley, C. S. and Evans, J. M.: The Risk of Major Surgery in Patients with Coronary Artery Disease. Am. J. M. Sc. **227**: 624 (June), 1954.

Because of the increasing importance of coronary artery disease in patients subjected to surgical procedures the authors have summarized the morbidity and mortality observations in 32 patients undergoing 51 major operations over a three year period. In 17 of the patients with myocardial infarction there were three deaths, each of which was attributable to the presence of coronary artery disease. Two were due to recent myocardial infarction and one to congestive heart failure. An additional patient experienced auricular fibrillation which responded promptly to treatment. In 15 patients with angina pectoris there were no deaths while two developed congestive heart failure. It is agreed that 3 to 6 months should elapse following an acute myocardial infarction to permit repair of the heart muscle prior to operation. The authors feel that their figures reflect the improved outlook for the coronary artery disease patient undergoing surgery.

SHUMAN

Kourias, B.: The Treatment of Traumatic Aneurysms by Classical Methods. Angiology **5**: 235 (June), 1954.

The surgical experience at the Greek Red Cross Hospital with 32 arterial aneurysms and 26 arteriovenous fistulae is reviewed. The techniques employed included ligation, extirpation, obliterative endo-aneurysmorrhaphy and restorative endo-aneurysmorrhaphy. The author states that these older methods—as contrasted with venous and arterial grafting—are capable of producing satisfactory results in many instances.

WESSLER

De Bakey, M. E., and Cooley, D. A.: Treatment of Aneurysms of the Aorta by Resection and Restoration of Continuity with Aortic Homograft. Angiology **5**: 251 (June), 1954.

Twenty-nine patients with aortic aneurysms were treated by excision and replacement with aortic homografts. There were six deaths: three from coronary artery disease, two from progressive uremia and one from pulmonary embolism six weeks after discharge from the hospital. Most of the patients showed improvement of the circulation in the lower extremities following operation and all have had complete relief of symptoms. The follow-up period has, in general, been less than twelve months. For graft preservation the technique of freeze-drying is considered the method of choice. Several important technical details are briefly described.

WESSLER

DeBakey, M. E. and Cooley, D . A.: Successful Resection of Aneurysm of Distal Aortic Arch and Replacement by Graft. J.A.M.A. **155:** 1398 (Aug. 14) 1954.

Occlusion of the aorta, at or near the arch, for varying periods of time, carries the risk of ischemic damage to the spinal cord or to vital organs. The authors report resection of a fusiform aneurysm involving the distal portion of the arch of the aorta with restoration of normal blood flow by means of an aortic homograph. The fact this was done after hypothermia had been induced is of added interest. The feature deserving major consideration here is that there was no ischemic damage to the spinal cord or other vital organs after arrest of aortic circulation distal to the left common carotid artery for one hour's time. This would suggest that hypothermia is an effective means of prolonging the safe period for temporary arrest of the aortic circulation.

KITCHELL

Dubost, C., and Dubost, C.: Resection of Aneurysms of the Aorta. Angiology **5**: 260 (June), 1954.

Three cases are described in detail in which aortic aneurysms were resected and successfully replaced with grafts. The longest follow-up was three years.

WESSLER

THROMBOEMBOLIC PHENOMENA

Revill, R. D. and Wilson, W. C. MacC.: Thrombotic Microangiopathy. Brit. M. J. **1**: 81, (July 10), 1954.

The authors describe another case of this condition which goes by various denominations—in this country, mainly thrombotic thrombocytopenic purpura—and which is characterized by fever, acute hemolytic anemia, thrombocytopenia with purpura and other hemorrhagic manifestations, and fluctuating neurological signs. The morbid histology comprises widespread patchy thromboses of minute blood vessels. All reported cases so diagnosed have been fatal.

McKUSICK

Alergant, C. D.: Sudden Simultaneous Arterial Embolism Involving All Four Limbs. Brit. M. J. **1**: 86, (July 10), 1954.

In the patient described, 58 years old, a recent myocardial infarction had occurred but no intraventricular thrombi were discovered. The source was quite clearly large thrombi on atheromatous ulcerations of the ascending aorta; the formation of thrombi at that site may have been abetted by the hypotensive state accompanying the myocardial infarction.

McKUSICK

Wolff, F. W.: Shock Due to Pulmonary Embolism. Treatment with l-Noradrenaline. Lancet **2**: 72, (July 10), 1954.

The mechanism of death from pulmonary embolism is often shock, possibly of reflex origin. A case is described in which survival of the patient was attributed to the administration of the vasopressor agent. Acute gastric dilatation was a complication of the drug therapy.

McKUSICK

VASCULAR DISEASE

Kolff, W. J., Page, Irvine H., and Corcoran, A. C.: Pathogenesis of Renoprival Cardiovascular Disease in Dogs. Am. J. Physiol. **178**: 237 (August) 1954.

In intact dogs with a 29% increase in body weight due to overhydration, hypertension or vascular damage is not observed even when the urine is being deviated into the circulation. An equal hydration in the absence of the kidneys does elicit the disease. More damage is done if the overhydration occurs rapidly. The vascular lesions are intensified by an elevated blood pressure. A low sodium concentration of serum protects but a small increase is without effect. Sodium space for Na^{24} was increased even though that for deuterium was not. Spinal transec-

tion at C_6 had no effect on renoprival hypertension and vascular damage. The fact that renoprival dogs are susceptible to hypertension and vascular damage depends on the loss of a non-excretory function of the whole kidney.

OPPENHEIMER

Zimmerman, H. J., Kleitsch, W. P., Greene, A. M., and McFadden, H. F., Jr.: Periarteritis (Polyarteritis) Nodosa Producing Intussusception. Arch. Int. Med. **94:** 264 (Aug.) 1954.

Two patients with intussusception due to visceral angiitis of the cecum are described. In one patient the diagnosis of periarteritis nodosa was established by the clinical, laboratory, and histopathologic studies. In the other patient, the clinical and histological features, while not clearly those of periarteritis nodosa, were in the category of a "visceral angiitis".

The two patients presented here, however, illustrate that abdominal complications of visceral angiitis may at times produce true surgical emergencies. Perforation of a hollow viscus due to involvement by periarteritis nodosa has also been described, and this would constitute another example of a surgical emergency in this disease. Even segmental infarctions may lend themselves to surgical removal, permitting survival of a patient who might otherwise die.

BERNSTEIN

Schneewind, J. H.: The Walking Venous Pressure Test and Its Use in Peripheral Vascular Disease. Ann. Surg. **140:** 137 (Aug.) 1954.

The author studied walking venous pressures in the lower extremities in normal subjects and in patients with varicose veins, postphlebitic sequelae and arteriosclerosis obliterans. In normal individuals exercise caused a rapid and sustained fall in venous pressure and a quick return to control levels after termination of the physical effort. In the case of patients with varicosities, the drop was much less than normal. However, following vein ligation and stripping, it became more marked. In the case of the subjects suffering from postphlebitic sequelae, vein surgery also resulted in a greater fall in venous pressure than had been observed preoperatively.

ABRAMSON

Gottlieb, H. and Lalich, J. J.: The Occurrence of Arteriosclerosis in the Aorta of the Swine. Am. J. Path. **30:** 851 (July), 1954.

Fresh aortas were examined from over 2,000 swine varying in age from three months to four years. The percentage of aortas showing changes was quite small (3 per cent) in swine under one year of age and rose almost linearly to 35 per cent in swine over three years of age. The plaques were located usually in the descending arch or thoracic aorta. They were composed of fibrous connective tissue, and had little lipid material and no calcium precipitates.

HARVEY

Waddell, W. R., Sniffen, R. C., and Whytehead, L. L.: Influence of Blood Lipid Levels on Inflammatory Response in Lung and Muscle. Am. J. Path. **30:** 757 (July), 1954.

In a series of well controlled experiments a pneumonitis was established by inoculation intratracheally of *Klebsiella pneumoniae* and *Pasteurella pseudotuberculosis* in normal rabbits and in rabbits with high serum lipid levels produced by cholesterol feeding. The pneumonitis was identical qualitatively in the two groups, but in the rabbits with high serum lipid levels, tremendous quantities of lipid were deposited in the inflamed areas and was taken up by phagocytes. In a similarly fed two groups of rabbits, a muscle was made ischemic by ligation of its nutrient artery and stripping of its sheath. Again in the necrotic lesion lipid deposition occurred, but it was much greater in those rabbits with high serum lipid levels. The authors suggest this process is dependent upon local physicochemical stability and not on high serum lipid levels per se, except that this influences the reaction quantitatively.

HARVEY

Williams, A. A.: Malignant Disease Associated with Vascular Phenomena. Brit. M. J. **1:** 82 (July 10), 1954.

The author describes four cases of Trousseau's syndrome, recurrent phlebitis migrans in association with visceral carcinoma, and one case of Raynaud's syndrome with carcinoma of the stomach. The latter is a rare but seemingly *bona fide* association. The cause of the Trousseau syndrome was carcinoma of the lung in three cases and of the head of the pancreas in one. The author believes that blood-borne neoplastic cells initiated these thromboses; the formation of thrombi about the cells probably results in their death.

MCKUSICK

Cairns, A. and Constantinides, T.: Mast Cells in Human Atherosclerosis. Science **120:** 31 (July 2), 1954.

The authors had previously found an inverse correlation between the tissue mast-cell content and susceptibility to alimentary lipemia or atherosclerosis. This report is a quantitative study of mast cells in human hearts. The cells were counted in toluidine blue stained sections from the myocardium of 46 young adults under the age of thirty-five, 48 elderly adults with marked generalized atherosclerosis over age sixty, and 48 elderly individuals without gross evidence of atherosclerosis. The cases were evenly divided by sex. Counts were made without knowledge of the identity of the samples.

The results indicate that atherosclerotic senile individuals had a lower count than nonatherosclerotic young adults. There was no significant difference between the nonatherosclerotic young or old adults. Furthermore, there was a statistically sig-

nificant difference between young female adults and elderly atherosclerotic females.

According to the authors, the only common features of each group were the presence or absence of atherosclerosis, the sex, and, within broad limits, the age. They believe that there are indications that the tissue mast-cell concentrations are influenced by the adrenal and other hormones and that it is possible that variable conditions of endocrine imbalance may account for the variations found within each group.

WAIFE

Blumenthal, H. T., Handler, F. P., and Blache, J. O.: The Histogenesis of Arteriosclerosis of the Larger Cerebral Arteries, with an Analysis of the Importance of Mechanical Factors. Am. J. Med. **17:** 337 (Sept.) 1954.

The histogenesis of cerebral arteriosclerosis has been studied in the basilar arteries of 124 patients ranging in age from newborn to ninety-three years. This has been supplemented by gross examination of 37 circles of Willis in which locations of placques have been mapped, internal and external diameters measured, and vascular anomalies recorded. Differences in histologic pattern of development of arteriosclerosis in the basilar artery from patterns observed elsewhere are in large part determined by certain inherent weaknesses of the wall characteristic of cerebral arteries, and account for the considerably higher incidence of aneurysm and rupture than occurs elsewhere. Measurements of the internal and external diameters of arteries have permitted calculation of effective hydrostatic tensions in various locations in the circle of Willis. The calculated tensions have been correlated with degrees of dilatation and thickening of the wall with age, and with the frequency of placque formation.

From such data and the histologic studies a concept has been derived that arteriosclerosis is fundamentally an adaptive response, structural as well as biochemical, to mechanical factors, in which all layers of the arterial wall are involved. Some physical factors are of general type, others local in character. Alterations in arteries which lead to the development of arteriosclerosis are of an adaptive nature which tend to minimize the increase in internal diameter produced by hydrodynamic factors acting over long periods of time. The investigators observe that mechanical factors act to stimulate the new formation of certain tissue elements, and the breakdown of other structures with local release of metabolites, particularly lipids, which may remain in the vessel wall.

HARRIS

Ochs, L., Sensenbach, W., and Madison, L.: Primary Thrombosis of the Internal Carotid Artery. Am. J. Med. **17:** 374 (Sept.) 1954.

The authors review the literature of primary thrombosis of the internal carotid artery and report seven new cases with cerebral circulatory and metabolic studies. Atherosclerosis is the commonest cause of this condition. The left internal carotid artery is more frequently involved by spontaneous thrombosis than is the right. There are four reasonably well defined clinical syndromes associated with spontaneous thrombosis of the carotid arteries in the neck: (1) The onset of symptoms may be sudden and acute, in which case the clinical picture usually closely simulates that of an intracerebral vascular lesion. Careful palpation of the vessels in the neck may provide the clue to the extracerebral location of the lesion. (2) The onset of symptoms may be insidious with transient episodes of visual disturbances, hemiplegia, monoplegia, aphasia, etc., with a slowly progressive course over a period of months or years, resembling the course of an expanding intracranial lesion. (3) If a thrombus in the internal carotid artery extends to involve and occlude the ophthalmic artery, homolateral blindness and contralateral hemiplegia may result. (4) Thrombosis of the internal carotid artery may occur silently without significant disabling or localizing signs.

Cerebral circulatory studies in these seven patients did not reveal hemodynamic or metabolic changes that could be convincingly attributed to unilateral internal carotid artery thrombosis alone. However, others have shown that the interruption of blood flow through one internal carotid artery is accompanied by an increase in cerebral vascular resistance. The investigators found that neurologic sequelae in internal carotid artery thrombosis occur only when this increment in cerebral vascular resistance is superimposed upon a pre-existing increase in cerebral vascular resistance of sufficient magnitude to reduce cerebral blood flow to a level which is insufficient to maintain the structural integrity of the entire brain.

HARRIS

Berthond, E. and Mottu, T.: The Treatment of Ischemic Disorders of the Lower Limbs by Intraarterial Histamine Infusions. Acta cardiol. **9:** 189 (Fasc. 3), 1954.

Thirty patients suffering from ischemic disturbances of the lower extremities were treated by repeated intraarterial infusions of histamine phosphate according to the method of Mufson. No serious incident occurred during the course of the intraarterial infusion. Improvement in the ability to walk was striking in ten out of twelve subjects with uncomplicated intermittent claudication. When the claudication was associated with pain at rest (two cases) or by infection in the extremities (two cases) the treatment had a beneficial effect on the complication, but none on the claudication. In the presence of frank (2 cases) or imminent (12 cases) gangrene, the results of treatment were generally disappointing. The indications for various other

therapeutic procedures in ischemic disturbances of the lower extremities are briefly discussed.

PICK

OTHER SUBJECTS

Moore, W. F.: Cardiac Involvement in Progressive Muscular Dystrophy. J. Pediat. **44:** 683 (June), 1954.

This is a case report of a white male who developed progressive muscular dystrophy at the age of seven and succumbed at the age of thirteen. He had signs of cardiac involvement with decompensation for one year prior to death. The propensity to tachycardia and arrhythmia is discussed. An autopsy report is included.

HARVEY

Hallenbeck, G. A. and Bruwer, A.: Portal Venography. Proc. Staff Meet. Mayo Clinic. **29:** 333 (June), 1954.

Methods are described for portal venography, accomplished by injection of radiopaque material either percutaneously into the spleen (the splenic portagram) or into a branch of the portal venous system during laparotomy (the portal portagram). Examples are described that illustrate the usefulness of these procedures to the surgeon contemplating the performance of portacaval shunting.

SIMON

De Langen, C. D.: The Placenta as an Example of the Peripheral Heart. Cardiologia **24:** 346 (Fasc. 6), 1954.

The author raises the question of the mechanism of placental circulation and doubts the validity of concepts ascribing maintenance of the foetal circulation to the contraction of the embryonic heart. The villi of the placenta show peristaltic movements but these are not synchronized with the pulsations of the placental arteries originating in the foetus, and occur independently from the contractions of the maternal heart. It is unconceivable that the small recently developed foetal heart could develop such a pumping force as to drive the blood through the capillaries of the foetus, to the umbilical cord, and back through the liver capillaries to the heart. It must therefore be assumed that potential, possibly chemical, energy of the placental villi is in some way converted to kinetic energy which makes possible the complex foetal circulation. There is no vasomotor system involved to assist this process because the foetal side of the placenta and the umbilical cord do not possess a nervous system.

PICK

Ross, D. N.: Venous Cooling, A New Method of Cooling the Blood-Stream. Lancet **1:** 1108 (May 29), 1954.

Surface cooling as a method for producing hypothermia carries with it risks of damage to skin, subcutaneous tissues such as fat, and nerves. Rate and depth of cooling are difficult to control. A secondary drop in body temperature, owing possibly to relief of peripheral vasoconstriction and perfusion of cold surface tissues may occur when the source of cold is removed.

Cooling of the arterial blood in an extracorporeal circuit obviates many of these difficulties but has the disadvantage that its efficiency is considerably dependent on cardiac output. As output falls with drop in temperature further lowering of temperature is effected with difficulty. Furthermore the arteriovenous fistula necessary for arterial cooling is likely to lower diastolic pressure and in instances of congenital malformation the latter phenomenon may aggravate right-to-left shunt.

The method the author describes involves leading blood from the superior vena cava, passing it through a cooling medium and returning it to the saphenous vein. An adult patient who was maintained at 26° C for one hour recovered without complications from closure of an atrial septal defect.

MCKUSICK

Chinard, F. P. and Enns, T.: Relative Rates of Passage of Deuterium and Tritium Oxides Across Capillary Walls in the Dog. Am. J. Physiol. **178:** 203 (August) 1954.

The diffusion constants of deuterium and tritium oxides in water are similar. Since the self-diffusion constant of water may be much greater than those of deuterium and tritium, it is not possible to conclude that the use of these two substances as tracers for water is valid.

OPPENHEIMER

Koletsky, S. and Gustafson, G. E.: Tourniquet Shock in Rats. Reversibility in the Terminal Phase. Am. J. Physiol. **178:** 229 (August) 1954.

Tourniquet shock was produced in rats when moribund; replacing the tourniquet did not prevent death. Saline infusion produced a temporary improvement and prolonged life. There was a temporary rise in blood pressure and an increased concentration of red cells in blood. Much of the fluid given appeared in the injured leg. If replacement of the tourniquet was combined with administration of saline there was a rapid improvement in the rat's condition.

OPPENHEIMER

Hammond, E. C. and Horn, D.: The Relationship Between Human Smoking Habits and Death Rates. J.A.M.A. **155:** 1316 (Aug. 7) 1954.

Death rates among 187,766 white men between the ages of 50 and 69 were studied in 1952. Their smoking histories had been obtained in 1951 by volunteer workers in 394 counties from 9 states of this country. The study areas covered large cities, smaller communities and rural districts. It was found that men with a history of regular cigarette

smoking have a considerably higher death rate than men who have never smoked or men who have smoked only cigars or pipes. A total of 3,002 deaths occurred among men with a history of regular cigarette smoking. If they had died at the same rate as men who never smoked, only 1,980 would have died. So 1,022 additional deaths (52% above expectancy) occurred among regular smokers of cigarettes. A breakdown of causes of deaths suggests that 56% of the total effect of regular cigarette smoking on the overall death rate may be attributed to the effect on diseases of the coronary arteries. Approximately 26% of the total effect of cigarette smoking on the over-all death rate may be attributed to the effect of cigarette smoking on deaths from cancer. The death rate from lung cancer was much higher among men with a history of regular cigarette smoking than among men who never smoked regularly. Regular cigarette smokers also had a higher death rate from cancer of sites other than the lungs than did men who never smoked. The authors feel a cause and effect relationship has been established between regular cigarette smoking and diseases of the coronary arteries and between such smoking and lung cancer. More information is needed before such statements of relationships can be made about cancer of sites other than the lungs and other diseases.

KITCHELL

Geckleler, G. D., Likoff, W., Mason, D., Riesz, R. R., and Wirth, C. H.: Cardiospectrograms. A Preliminary Report. Am. Heart J. **48**: 189 (Aug.) 1954.

In general, spectrum analysis is a procedure whereby a measurement is made which considers the energy distribution of a physical occurrence as a function of time and frequency. The sound spectrograph, as widely used in speech research, produces patterns that show the frequency components present in audible sounds. A preliminary report is presented of a new application of spectrum analysis, cardiospectrograms, in which a graphical-spectrum display is made of heart sounds.

Although the technique is still being modified, records of certain typical cardiospectrograms were presented and discussed. Normal heart sounds presented a wide variety of patterns. In general, however, visual portrayal of these sounds shows that the low component of the first sound predominates in some individuals but not in others; that the length of the sounds does not differ so much as one's audible experience leads one to think; and that a third sound is often seen when it cannot be heard. Another point of interest concerned the analysis of presystolic "crescendo" murmurs. The spectrographic analysis demonstrates no increase in loudness of the murmur as it develops nor increasing predominance of the low end which might make the murmur sound louder as it progresses up to the first sound. The sharp element of the apical first sound associated with this murmur apparently is always short and high-pitched, lacking a predominance of low frequencies, and it is these features which characterize it as "sharp."

It is felt that the technique will be considerably improved and its uses expanded.

MAXWELL

BOOK REVIEWS

An Atlas of Congenital Anomalies of the Heart and Great Vessels. *J. E. Edwards, T. J. Dry, R. L. Parker, H. B. Burchell, E. H. Wood and A. H. Bulbulian.* Springfield, Ill. Charles C Thomas, 1954. 202 pages, 256 figures, 45 in color. $13.50.

This monograph is an expanded version of "Congenital Anomalies of the Heart and Great Vessels." published in 1948. It summarizes the experience of physicians working at the Mayo Clinic. Twenty-nine malformations are described beginning with cor biloculare, the most primitive type of heart, and ending with anomalies of the aortic arch, coronary arteries and coronary sinus. Each section contains a summary of the anatomic features and clinical characteristics of the lesions described. Case reports are then presented, chosen to include complications and anatomic variations that have come under the observation of the authors. In a limited number of cases it has been possible to include data obtained by cardiac catheterization, oximetry, dye-dilution methods and intra-arterial pressure studies.

The illustrations are excellent and include photographs of gross anatomic specimens and pertinent microscopic sections, diagrams of the intracardiac circulation as well as reproductions of available roentgenograms of the chest and electrocardiograms. Diagrams have also been used to clarify the possible anatomic variations of certain lesions (tricuspid atresia with and without transposition of the great vessels, persistent truncus arteriosus) or the developmental basis of others (cor triatum). Of particular interest are photographs illustrating structural changes in the intrapulmonary muscular arteries in conditions in which a relatively high resistance of blood flow in the lungs is essential to prevent flooding of the lesser circulation (normal fetus, single ventricle with subaortic stenosis, Eisenmenger complex).

Although the book on the whole contains only material that has come under the personal observation of the authors a bibliography is included which covers many of the important references to the lesions described as well as to the general subject of cardiovascular anomalies.

At the end of the book there is a section devoted to brief biographic sketches of 16 physicians who have made important observations in the field of congenital heart disease. There is also an adequate index.

The book presents a wealth of material in concise form and there are few adverse critical comments that may be offered. In a field in which information is being accumulated so rapidly, it is unfortunate that there are no references to work published later than 1951. Surgical treatment is mentioned only when operation has chanced to be performed in individual cases. Among other omissions there is no mention of the feasibility of closure of atrial septal defects or of the correction of anomalous drainage of pulmonary veins. A discussion of possible corrective surgical procedures and of indications for operation might well be added to the initial descriptive summary of each malformation. It is probably an oversight in the discussion of complete anomalous drainage of pulmonary veins that the similarity of the oxygen saturation of the blood in the right atrium and the systemic circulation is not mentioned. A clinical case such as the "Eisenmenger Complex" on page 72 in which the diagnosis has not been proven by necropsy or operation should not be included. The authors accept the statement frequently found in the literature that congenital heart block occurs in association with ventricular septal defect. In reported cases studied by serial sections however the break in continuity of the conducting tissue has been found in the absence of a ventricular septal defect and may be considered an independent developmental malformation. It is extremely rare for the usual type of ventricular septal defect to be associated with congenital heart block.

This monograph will be desired by all physicians who admire fine books of artistic quality. It will be of value as a concise source of reference to all those interested in the subject of congenital cardiovascular anomalies.

R. Ash

Hypertensive Diseases—Causes and Control. *Henry A. Schroeder, M.D., F.A.C.P.* Philadelphia, Lea & Febiger, 1954. 610 pages, 164 figures, 3 color plates, 106 tables. $10.00.

Dr. Schroeder's book is a highly personalized account of the current status of the hypertensive states, by a physician who has not only witnessed the unfolding of present-day concepts of pathogenesis and treatment, but has participated actively in their development.

The author states as a premise that his book is based upon a "conviction fostered by experience and nurtured by knowledge that 'essential' hypertension is not a single disease." The organizational pattern of the book consequently reflects a perspective of hypertension as a group of diseases which involve to a varying degree the interplay of five essential elements, broadly grouped into constitutional, psychogenic, neurogenic, nephrogenic and hormonal categories. The first third of the book is devoted to a consideration of these elements as they enter into the etiology and pathogenesis of the hypertensive states. This is supplemented by dis-

cussions of the factors responsible for the physiological regulation of blood pressure, the possible roles of nitrogen compounds (principally the amines) in the vasoconstrictive mechanism, and the effects of chronic arterial hypertension on the organs and tissues. The second portion of the book uses the fundamental organizational pattern as the basis for detailed descriptions of the classification and recognition of different clinical types of hypertension, the stage of the disease and its rate of progress. The final third of the book again invokes the basic pattern, this time from the aspect of the treatment of the five essential elements, together with a separate consideration of the management of renal insufficiency. Approximately half of the section on therapy is devoted to the control of hypertension by Hyphex (the combination of hydralazine and hexamethonium chloride).

The content of the book deals almost exclusively with human data. The topic of experimental renal hypertension is limited to approximately 12 pages; experimental neurogenic hypertension is confined largely to a table listing the types of stimuli by which it may be caused; the existence of experimental adrenocortical hypertension is mentioned. It may be regrettable to some that the wealth of literature dealing with systematic studies of animal hypertension has not been applied more liberally to clarify and synthesize the more obscure aspects of the human disease. In contrast, experimental data derived from clinical investigations are presented and discussed in detail, and a considerable effort has been expended in attempting to correlate and reconcile conflicting lines of evidence and points of view in order to achieve a logical and consistent presentation.

The aspects of the book which may provoke the greatest number of exceptions are the relative emphasis and value assigned to various forms of therapy. Sympathectomy is discussed in less than five pages, while adrenalectomy is dismissed in 11 lines. The rauwolfia alkaloids receive one paragraph. In contradistinction, 70 pages are devoted to treatment by Hyphex. Many physicians whose more limited experience may have unduly accentuated the therapeutic failures, the frequent and occasionally unendurable side effects, the high cost to the patient and the adverse psychological effects of a prospect of unending multiple pill-taking, may find themselves more restrained in their enthusiasm and less optimtisic about currently available hypotensive drugs.

Despite these criticisms (the kind which no book on hypertension may avoid, in view of the controversial nature of the subject and the varying interests of the audience), most readers will find Dr. Schroeder's work provocative, interesting and helpful, and a desirable addition to the bookshelf.

D. M. GREEN

Physiology in Diseases of the Heart and Lungs. *M. D. Altschule, M.D.* Cambridge, Mass., Harvard University Press, 1954. 554 pages. $7.50.

This book presents in condensed form most of the significant information which has been obtained in recent years on selected subjects in the pathologic physiology of heart and lung disease. The heart is given more attention than the lungs. The extent of condensation is such that the bibliography pertaining to many topics occupies more space than the author's summary of existing knowledge in the field. To be as lucid and coherent as they are, these summaries must necessarily be constructed around the author's concepts of what the data mean. Consequently, most experienced readers will find themselves in frequent disagreement, though by no means always at the same places. Such disagreements are in themselves enlightening and entertaining.

For the investigator who is working in these areas, the book is a valuable source of references. Even in a rapid reading the reviewer found several new pieces of information directly pertinent to his present interests. For the student the book is a brief, skillful interpretation of a very large quantity of experimental data and, taken altogether, a very fair presentation of present-day concepts. It is a most useful book for anyone who is seriously interested in heart and lung disease.

JOHN B. HICKAM

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ABSTRACT DEADLINE FOR AHA ANNUAL MEETING IS JULY 1

July 1 is the deadline for submission of abstracts of papers to be presented at the 1955 AHA Annual Meeting and 28th Scientific Sessions to be held at the Jung Hotel in New Orleans, October 22–26. The three-day scientific programs are to be presented on October 22, 23 and 24.

Abstracts should be of 300 words or less and submitted in duplicate to the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

The Scientific Sessions will be conducted by the various sections and councils of the Association's Scientific Council, including the Section on Basic Science, the Section on Circulation, the Section on Clinical Cardiology, the Section on Cardiovascular Surgery and the Council for High Blood Pressure Research. A program will be presented by the Council on Rheumatic Fever and Congenital Heart Disease and a special program will be jointly conducted by the rheumatic fever council and the Council on Community Service and Education. The plans of the latter council also call for the presentation of its own program on nutrition and rehabilitation.

The Annual Dinner of the Association is to be held on Monday evening, October 24. The Assembly, top governing body of the Association, will hold its panel discussions on Tuesday, October 25, and its annual meeting on Wednesday, October 26.

Arrangements are now being made for special exhibits at the Hotel, and for a post-meeting medical tour of Mexico for physicians.

APPLICATIONS FOR AHA RESEARCH SUPPORT NOW BEING ACCEPTED

Applications by research investigators for support of projects to be undertaken during the fiscal year beginning July 1, 1956 are now being accepted by the Association.

The application deadline for research fellowships and established investigatorships is September 15, 1955. Applications for grants-in-aid must be made by November 1, 1955, *a month earlier than in previous years.*

Funds for Heart Association support of research projects in the cardiovascular field are provided by public contributions to the Heart Fund. More than $11,800,000 has been allotted to research by the National Office and by affiliates since the reorganization of the AHA as a voluntary health agency in 1948.

Applications may be made for awards in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,000 to $9,000 yearly, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators.

Research Fellowships: Awarded to young men and women with doctoral degrees for periods of one to two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,500 to $5,600.

Grants-in-Aid: Made to experienced investigators to provide support for specified projects. Grants are made in varying amounts not to exceed $10,000.

The Association also maintains another and unique form of research support, the Career Investigatorship. This is given to a limited number of investigative scientists of unusual capacity and accomplishment to assure them of financial support throughout their productive lives. Career investigators are selected on the initiative of the Research Committee, and not by application.

Further information and applications may be obtained by writing to the Medical Director, American Heart Association, 44 East 23 Street, New York 10.

AUDIO-VISUAL KIT FACILITATES HOME STUDY

"Cardiac Clinics," a newly devised audio-visual kit is now available to physicians through their Heart Association. Contained in the kit are a medical discussion, recorded on 33⅓ rpm, long-playing discs, and accompanied by a script of the discussion, correlated 2″ x 2″ slides and a table-top viewer for the slides.

The kit is designed primarily for home or office use and is intended particularly for physicians who do not have educational facilities readily available. It can also be used in small meetings by adding projection and sound amplification equipment.

The initial kit in the series is "The Role of the PA Film of the Chest in Cardiology," prepared by Dr. William R. Christensen, Professor of Radiology, University of Utah College of Medicine. It is now available through the Association and its affiliates.

NEW "CARDIO-VIEWS" KITS UTILIZE 3-D PHOTOGRAPHY

The first of a new series of three-dimensional visual kits, designed for use in teaching and in individual study is now being prepared by the Medical Division. The kits utilize stereoscopic photography and a simple viewer for 3-D slides. They will be known as "Cardio-Views."

The first in the series of kits illustrates each of 12 heart models, presenting PA, RAO and LAO views with corresponding silhouettes imprinted above on 16mm. stereoscopic color film. There are 36 views in all.

MEETINGS CALENDAR ABROAD

June 13–18: American Society for Pediatric Research, Québec City, P.Q. Sydney S. Gellis, 330 Brookline Avenue, Boston 15.

June 18–19: Fifth Congress of the International Association for the Study of the Bronchi, Stockholm, Sweden. Dr. Stahle, Kohlmarsanatoriet, Sweden.

June 20–22: Canadian and British Medical Associations, joint meeting, Toronto, Canada. Dr. Arthur D. Kelly, 244 St. George Street, Toronto.

June 21–25: Commonwealth Health and Tuberculosis Conference, Royal Festival Hall, London, England. Mr. J. H. Harley Williams, Tavistock House North, Tavistock Square, London W.C.1.

July 4–8: Congress of the International Diabetes Federation, Cambridge, England. James G. L. Jackson, Diabetic Association, 152 Harley Street, London W.C.1.

July 23–29: Sixteenth Congress of the International Society of Surgery, Copenhagen, Denmark. Dr. L. DeJardin, 141 rue Delliard, Brussels, Belgium.

July 25–30: International Anatomical Congress, Paris, France. Professor Gaston Cordier, 45 rue des Saint-Pères, Paris 6e.

August 1–6: International Congress of Biochemistery, Brussels. Professor C. Liebecq, 17 Place Delcour, Liège, Belgium.

August 14–20: Pan-American Congress of Rheumatic Diseases, Rio de Janeiro and São Paulo Brazil. Dr. Waldemaar Bianchi, 126 Avenida Franklin D. Roosevelt, Rio De Janeiro.

September 2–5: International Congress of Angiology and Histopathology, Fribourg, Switzerland. Professor A. Müller, Institute of Physiology, University of Fribourg, Switzerland.

September 12–17: International Congress of Neuropathology, London. Dr. W. H. McMenemey, Department of Pathology, Maida Vale Hospital, London W. 9.

September 20–26: Ninth General Assembly of the World Medical Association, Vienna, Austria. Jean Mignon, Le Concours Médical, 37 rue de Bellefond, Paris 9e.

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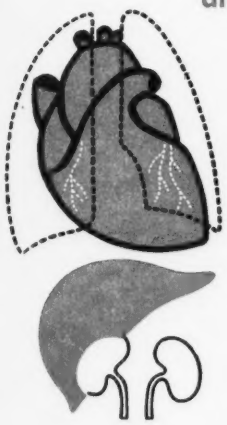

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CONTENTS

INDEX ISSUE

ELECTRIC ALTERNANS IN PERICARDIAL EFFUSION
Maurice McGregor and Eugene Baskind 837

CHRONIC EFFUSIVE PERICARDITIS ..... *S. Contro, G. DeGiuli and F. Ragazzini* 844

ON CARDIOVASCULAR SOUND. FURTHER OBSERVATIONS BY MEANS OF SPECTRAL PHONOCARDIOGRAPHY
Victor A. McKusick, George N. Webb, J. O'Neal Humphries and James A. Reid 849

THE SIGNIFICANCE OF THE SERUM GLUTAMIC OXALACETIC TRANSAMINASE ACTIVITY FOLLOWING ACUTE MYOCARDIAL INFARCTION
John S. La Due and Felix Wróblewski 871

DIRECT ARTERIAL STUDY OF THE BLOOD PRESSURE RESPONSE TO COLD OR NORMOTENSIVE SUBJECTS AND PATIENTS WITH ESSENTIAL HYPERTENSION BEFORE AND DURING TREATMENT WITH VARIOUS ANTIHYPERTENSIVE DRUGS
John H. Windesheim, Grace M. Roth and Edgar A. Hines 878

BLOOD PRESSURE RESPONSES TO THE VALSALVA MANEUVER IN CARDIAC PATIENTS WITH AND WITHOUT CONGESTIVE FAILURE
Walter E. Judson, J. D. Hatcher and Robert Wilkins 889

STUDIES OF CIRCULATION TIME DURING THE VALSALVA TEST IN NORMAL SUBJECTS AND IN PATIENTS WITH CONGESTIVE HEART FAILURE
Paul Stucki, J. D. Hatcher, Walter E. Judson and Robert W. Wilkins 900

ARTERIOSCLEROTIC OCCLUSION OF CEREBRAL ARTERIES: MECHANISM AND THERAPEUTIC CONSIDERATIONS ..... *Walter L. Bruetsch* 909

NORMAL STANDARDS FOR AMPLITUDE OF BALLISTOCARDIOGRAMS CALIBRATED BY FORCE ..... *Isaac Starr* 914

THE ELECTROCARDIOGRAPHIC PATTERN OF RIGHT VENTRICULAR HYPERTROPHY IN CHRONIC COR PULMONALE. *Ralph C. Scott, Samuel Kaplan, Noble O. Fowler, Robert A. Helm, Richard N. Westcott, Isom C. Walker and William J. Stiles* 927

MEASUREMENT AND SIGNIFICANCE OF CANCELLATION POTENTIALS ON THE HUMAN SUBJECT ..... *Ernest Frank* 937

THE EFFECTS OF REPETITIVE ELECTRIC CARDIAC STIMULATION IN DOGS WITH NORMAL HEARTS, COMPLETE HEART BLOCK AND EXPERIMENTAL CARDIAC ARREST ..... *T. E. Starzl, R. A. Gaertner and Roscoe C. Webb, Jr.* 952

CLINICAL PROGRESS. PRIMARY TUMORS OF THE HEART
Henry P. Goldberg and Israel Steinberg 963

ABSTRACTS 971

BOOK REVIEWS 993

AMERICAN HEART ASSOCIATION 995